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SUCCESSFUL AUTOTRANSPLANTATION OF THE ADRENAL GLAND IN THE DOG

JOHN L. KEELEY, M.D.

J. ENGLEBERT DUNPHY, M.D.

T. B. QUIGLEY, M.D.

AND

JOHN FRYE BELL, M.D.

BOSTON

Autotransplantation of the adrenal gland in the rat and in the guinea pig has been reported by a number of investigators.[1] However, it is generally accepted that such a graft undergoes partial necrosis which is followed by regeneration of cortical tissue only. A successful transplantation of the whole adrenal gland in small animals has not been described.

Crowe and Wislocki[2] were among the first to attempt to transplant the adrenal in the dog. They observed that when fragments of the gland were placed in muscle only the cortical tissue survived. Such transplants were found to be functionless. Oldberg[3] and Blodinger and his co-workers[4] also were unable to obtain functioning autogenous grafts of the adrenal in the dog. Recently, however, Levy and Blalock[5]

From the Laboratory of Surgical Research and the Department of Surgery of the Harvard Medical School.

1. Jaffe, H. L.: Transplantation of the Guinea Pig Suprarenal and Functioning of Grafts, J. Exper. Med. **45**:587, 1927. Wyman, L. C., and tum Suden, C.: Studies on Suprarenal Insufficiency: Growth of Transplanted Cortical Tissue in Rat, Am. J. Physiol. **101**:662, 1932. Ingle, D. J., and Higgins, G. M.: Autotransplantation and Regeneration of Adrenal Gland, Endocrinology **22**:458, 1938.

2. Crowe, S. J., and Wislocki, G. B.: Experimental Observations on Suprarenal Glands with Special Reference to the Functions of Their Interrenal Portions, Bull. Johns Hopkins Hosp. **25**:287, 1914.

3. Oldberg, E.: An Attempt to Transplant the Adrenal, Am. J. Physiol. **91**:225, 1929.

4. Blodinger, I.; Klebanoff, H. E., and Laurens, H.: Suprarenal Transplantation in the Dog, Am. J. Physiol. **76**:151, 1926.

5. Levy, S. E., and Blalock, A.: A Method of Transplanting the Adrenal Gland of the Dog with Reestablishment of Its Blood Supply, Ann. Surg. **109**:84, 1939.

have reported transplantation of the kidney together with the adrenal to the neck (with reestablishment of the blood supply by suture of vessels) and subsequent removal of the kidney. In their preparations both the cortex and the medulla of the adrenal remained viable. The method of transplanting the adrenal gland described here resembles that of Levy and Blalock [5] in that viable grafts of both the cortex and the medulla were obtained. This was accomplished, however, by grafting the adrenal to the ovary without suture of blood vessels.

MATERIAL AND METHOD

The general procedure was as follows: Mongrel bitches weighing between 5 and 10 Kg. were used in all experiments. The operations were performed aseptically with the animals under intravenous sodium pentobarbital anesthesia. The adrenal was approached through a transperitoneal upper right rectus or oblique subcostal incision. By careful dissection the lower pole of the adrenal gland was partially mobilized. The neurovascular connections to the remainder of the gland were not disturbed. In none of the preparations was the lumbo-adrenal vein ligated or separated from the adrenal gland at this stage. The ovary on the experimental side was then mobilized and drawn up to the adrenal, care being taken not to interfere with its vascular supply. The ovarian bursa was incised, the ovary being exposed. A small portion of both ovary and adrenal was then excised so as to create raw bleeding surfaces, which were united by mattress sutures of fine silk. At a second operation, two to four weeks later, the adrenal was separated from its remaining normal neurovascular connections and, together with the adherent ovary, was brought into the peritoneal cavity. Its position there was maintained by suturing it to the anterior abdominal wall. Excision of the opposite adrenal gland was performed either before or after the final transplantation, usually as a separate procedure. Variations of this procedure and the results obtained are shown in the accompanying table. It will be noted that whenever the vascular supply of the adrenal was divided at the first operation the experiment failed. It is necessary first to furnish the adrenal with a new blood supply through the ovary and then to separate it from its normal neurovascular supply.

RESULTS

Twelve experiments were performed, 4 of which were successful. Several factors account for the 8 failures. Experience with the operative technic is essential. Operation in stages not only permits the establishment of a new blood supply from the ovary to the adrenal but minimizes operative shock. As already noted, all attempts to accomplish grafting and division of the blood supply of the adrenal in one stage failed (experiments 1, 2, 3 and 10). The method of joining the adrenal to the ovary is of considerable importance. In the early experiments this was accomplished by excising a small fragment of both adrenal and ovary and then uniting the raw surfaces with mattress sutures. In only 2 of 5 attempts (experiments 4, 5, 6, 7 and 8) was the new vascular supply sufficient to maintain the life of the graft. In 3 instances the glands were partially bisected and the cut edges interlocked, or "sandwiched," together. This "sandwich" method proved more efficacious.

Procedure	Experiment No.	Survival Period	Result	Comment
Two stage operations 1. Right adrenalectomy 2. Mobilization and grafting of left adrenal (neurovascular supply of adrenal divided)	1	7 days	Failure	All attempts to divide blood supply to adrenal at same time that it was attached to the ovary failed
	2	1 day	Failure	
	3	9 days	Failure	
Three stage operations 1. Mobilization of right adrenal and grafting to ovary (adrenal blood supply left intact) 2. Left adrenalectomy 3. Grafted adrenal separated from its normal vascular supply and brought into the peritoneal cavity	4	9 days	Failure	
	5	Living 15 months after last operation	Success	
Three stage operations 1. Bilateral mobilization and grafting of adrenals to ovary (adrenal vascular supply left intact) 2. Excision of one graft and ovary 3. Separation of remaining graft from its normal vascular supply and transplantation into the peritoneal cavity	6	Died after 2d stage operation	Failure	
	7	9 days	Failure	
	8	10 months; killed (died 5 days after excision of transplant)	Success	Physiologic activity of graft proved by death of the animal from adrenal insufficiency
Three stage operations 1. Right adrenalectomy; left adrenal mobilized and attached to ovary (adrenal blood supply intact) 2. Partial freeing of graft 3. Complete freeing of graft from its normal vascular supply	9	2 days	Failure	
One stage operations ("sandwich technic") Right adrenalectomy; Mobilization and grafting of left adrenal	10	6 days	Failure	Failure attributed to fact that vascular supply of gland was divided at time of grafting
Four stage operations ("sandwich technic") 1. Left adrenal grafted to ovary (blood supply intact ["sandwich technic"]; see text)	11	Living 14 months after last operation	Success	Physiologic activity of graft proved as in experiment 8; see text for details
2. Right adrenal grafted to ovary (blood supply intact ["sandwich technic"]; see text) 3. Right transplant separated from blood supply and together with ovary brought into peritoneal cavity 4. Excision of left adrenal and ovary	12	1 year; killed (died 10 days after excision of transplant)	Success	

Two of 3 attempts (experiments 10, 11 and 12) were successful, and the single failure can be ascribed to the fact that the entire procedure was performed in one stage.

It is interesting that in 2 of the 4 successful experiments (experiments 11 and 12) the opposite adrenal was not excised until after transplantation of the graft into the peritoneal cavity, so that at the time of transplantation there was no acute physiologic need for the graft. Similar exceptions to Halsted's [6] "law of deficiency" have been noted by Shambaugh [7] in working with the parathyroid and by Levy and Blalock [8] in experiments performed with the adrenal.

The 4 animals on which successful transplantations were performed have remained in good health for ten, twelve, fourteen and fifteen months respectively since the removal of the opposite adrenal gland. All have either maintained their original weight or gained weight. In 2 instances conclusive evidence of the activity of the cortical portion of the transplant was obtained when death from cortical insufficiency occurred in five and ten days respectively after excision of the grafted tissue (experiments 8 and 12). During this period the dogs showed anorexia and weakness, and there was a terminal fall in the level of blood chlorides and in the blood pressure. The observations at autopsy were those usually associated with adrenal insufficiency. There were ulcerations of the mucosa in the upper part of the gastrointestinal tract, marked congestion of the pancreas and moderate congestion of the kidneys and liver. The spleen was small and contracted. In 1 dog the thyroid was four to five times the normal size. The enlargement was symmetric, involved both lobes and grossly and microscopically had the appearance of a colloid goiter. There was no hyperplasia, cyst formation, hemorrhage or adenoma. No accessory or remaining adrenal tissue was found. Gross and microscopic examination of the pituitary showed no variation from the normal.

At the time of removal (experiments 8 and 12) the transplanted adrenal tissue was easily recognized. On cut section the medulla was somewhat reduced in size, but the sharp contrast between it and the cortex was well preserved. On microscopic examination (eosin–methylene blue and hematoxylin and eosin stains) the cells of both the cortex and the medulla appeared normal. There was no hypertrophy or hyperplasia. Ganglion cells and unmyelinated nerve fibers were seen in the capsule and medulla of the transplants. Myelinated nerves could not be demonstrated with certainty. This is in accord with the studies of

6. Halsted, W. S.: Auto- and Isotransplantation, in Dogs, of the Parathyroid Glandules, J. Exper. Med. **11**:175, 1909.

7. Shambaugh, P.: Autotransplantation of Parathyroid Gland in the Dog: Evaluation of Halsted's Law of Deficiency, Arch. Surg. **32**:709 (April) 1936.

Elliott,[8] who showed that after denervation of the adrenal there is a degeneration of myelinated nerve fibers up to their termination in the medulla. Similar observations were made by Hollinshead,[9] who noted that unmyelinated fibers persist after removal of the upper lumbar sympathetic chain and both splanchnic nerves and denudation of the adrenal. Such nerves probably arise from intrinsic ganglion cells. Levy and Blalock [5] found only unmyelinated nerves in transplanted adrenals. A layer of very vascular connective tissue joined the adrenal to the ovary. In the latter there were numerous young follicles, some of which appeared cystic.

The behavior of the animals in which transplantation has been successfully carried out has not been altered. Levy and Blalock [5] observed a normal pregnancy in a dog with a transplanted adrenal, but none of our animals have been in heat, perhaps because of the utilization of the ovaries in the autotransplantation. At the time of writing the blood pressure of these dogs is maintained at normal levels, and no significant variations of the "fasting levels" of sugar, nonprotein nitrogen, albumin, globulin, calcium and phosphorus in the blood have been noted. As the histologic observations indicate a successful transplantation of the entire gland, these animals should react physiologically in the same manner as do animals in which complete denervation of one adrenal and excision of the other have been performed. Further studies of the metabolism of these dogs, particularly in relation to the functional activity of the transplanted medulla, are in progress.

SUMMARY

A method is described of autotransplantation of the adrenal gland of the dog by grafting it to the ovary without suture of blood vessels. Twelve experiments were performed, 4 of which were successful in that the graft maintained the life of the animal after removal of the opposite adrenal. In 2 dogs the transplant was excised and was found to be composed of viable cells of both the cortex and the medulla. The activity of the cortical portion of the graft was proved. Further studies of the metabolism of these dogs, particularly in relation to the functional activity of the medullary portion of the graft, are in progress.

8. Elliott, T. R.: The Innervation of the Adrenal Glands, J. Physiol. **46**: 285, 1913.

9. Hollinshead, W. H.: The Innervation of the Adrenal Glands, J. Comp. Neurol. **64**:449, 1936.

MASTECTOMY

A CLINICAL PATHOLOGIC STUDY DEMONSTRATING WHY MOST MASTECTOMIES RESULT IN INCOMPLETE REMOVAL OF THE MAMMARY GLAND

N. FREDERICK HICKEN, M.D.
SALT LAKE CITY

Simple mastectomy is an operation frequently attempted but seldom accomplished. Bold as this declaration may seem, it is true.

Theoretically the term "mastectomy" indicates complete excision of the mammary gland and does not apply to incomplete removal, partial resection or subtotal ablation. In practice, however, the vast majority of so-called "mastectomies" accomplish nothing more than incomplete extirpation of the main mass of mammary tissue. While the surgeon aims to remove all of the mammary gland, he invariably leaves some of it behind to undergo either normal involution or pathologic change.

During the past three years, careful anatomic and histologic studies have been made of all breasts sent to the pathologic laboratories of several large hospitals. The mastectomies had been done by well trained surgeons, many of whom had had considerable experience in surgical treatment of the breast. In practically every instance no difficulty was encountered in demonstrating that the breast had been incompletely removed and remnants of mammary tissue left in the operative area. This is no criticism of the excellent technic and ability of the operating surgeons; rather, it emphasizes certain anatomic peculiarities of the breast. I myself was by far the most persistent offender.

Embryologically the breast represents a modified sebaceous gland which has assumed a highly specialized function. Its ultimate size, shape and ramifications depend largely on the age and physical status of the patient and the functional experiences of the gland. It is composed of fifteen to twenty lobules, each of which has a separate ductal opening on the surface of the nipple. As a general rule, six to eight of these lobules assume fully 95 per cent of the functional load, the remaining segments being small and poorly developed.

Accurate anatomic patterns of the lactiferous ducts can readily be obtained by means of roentgen studies with a contrast medium.[1] The mammograms give a clear visualization of the ducts, denoting their size,

1. Skiodan viscous for this purpose was supplied by the Winthrop Chemical Co., New York.

number, conformation and distribution (fig. 1). During the past three years more than 385 mammograms have been made, and the ramifications of the lactiferous ducts have been carefully studied.[2] It is evident that the mammary gland does not occupy a small localized area on the anterior wall of the chest. Instead, its ducts are widely distributed over the entire anterolateral aspect of the thoracic cage. In fully 95 per cent of cases the visualized ducts ascended into the axilla, and in some

Fig. 1.—Mammogram showing the injected lactiferous ducts passing around the pectoral muscles as they extend into the axilla. A fibroadenoma occupies the lower mammary segment.

instances they followed the brachial plexus and blood vessels into the apex of the axillary fossa. All obstetricians appreciate the frequency with which this axillary segment becomes swollen and engorged during the early phase of active lactation. In 15 per cent of cases the ducts were seen to pass downward and medially into the epigastric space, and

2. Hicken, N. F.: Mammography: The Roentgenographic Diagnosis of Breast Tumors by Means of Contrast Substances, Surg., Gynec. & Obst. **64**:593-603, 1937.

in 2 per cent they followed the lateral wall of the chest beyond the anterior borders of the latissimus dorsi muscle. In 2 instances the ducts were seen to cross the midsternal line, but in no instance were there anastomotic communications with the opposite breast.[3] It was surprising to see the frequency with which the injected ducts came in intimate contact with the overlying skin. This was particularly true of the lactating gland (fig. 2).

These mammographic studies clearly demonstrated that the lactiferous ducts spread over the entire anterolateral wall of the chest. It follows, therefore, that simple mastectomy requires denudation of an extremely

Fig. 2.—Breast after injection of the ducts with a contrast medium. Note how closely the large duct and its ramifications approach the skin. This represents the ramifications of only one lobule of the breast of a multipara during its quiescent state.

large part of the thoracic wall if all mammary structures are to be completely removed.

An appreciation of the anatomic distribution of the lactiferous ducts combined with observation of the conservative type of operation employed in the usual mastectomy suggested to me that in many instances only a portion of the mammary gland had been excised.

3. Hicken, N. F.: Mammography: The Preoperative Visualization and Diagnosis of Breast Tumors by Means of Contrast Roentgenograms, Nebraska M. J. **22**:211-214, 1937.

Incontrovertible evidence as to the incomplete removal of the breast was easily obtained by study of the excised specimens which were routinely sent to the pathologic laboratories. This was done by cannulizing each of the ducts as it opened on the surface of the nipple and injecting it with a solution of methylene blue. If the mammary gland had been removed in its entirety, the ductal system remained intact; hence none of the dye could escape. If, however, the lactiferous ducts had been severed or if a portion of a lobule had been left in situ, the colored solution escaped, thus accurately indicating the area of incomplete removal.

Seventeen breasts which were supposed to have been completely excised by "mastectomy procedures" were examined in this manner. There was not a single instance in which the mammary tissue had been removed in its entirety. In 94 per cent of cases the dye escaped in the subareolar zone, indicating that some of the breast had been left attached to the reflected skin flaps. The axillary segment had been incompletely removed in 88 per cent of cases, the sternal extension in 23 per cent and the epigastric ramifications in 11 per cent. It was found that in 75 per cent of the specimens there were multiple areas of incomplete removal, and in 3 instances the dye escaped from the entire periphery of the breast, indicating a most inadequate operation.

According to these studies, there were certain segments of the breast which the surgeon was prone to remove incompletely, namely, the axillary extension, the subcutaneous zone, the sternal segment and the epigastric ramifications.[4] These are demonstrated in figure 3.

It would seem that if the breast is sufficiently diseased to necessitate amputation every precaution should be exercised to see that all mammary tissue is removed. Occasionally, residual mammary tissue undergoes pathologic transformation, necessitating subsequent operations and even eventuating in adenocarcinoma. The following cases are representative.

REPORT OF CASES

CASE 1.—Mrs. F. J., a housewife 46 years of age, the mother of three children, entered the hospital because of a "rapidly growing lump in her right axilla." Fifteen years previously the right breast had been amputated because of painful "chronic cystic mastitis." Examination demonstrated a hard tumor mass measuring 1 inch (2.5 cm.) in diameter, situated in the anterior axillary fold (fig. 4). It was firmly adherent to the underlying pectoral muscles but was not attached to the skin. Beneath the pectoral muscles there were two indurated, nontender lymph glands. A radical exenteration of the axilla with removal of the pectoral muscles was performed. The tumor mass was found to consist of normal mammary tissue impregnated with adenocarcinoma which had spread to the regional lymph glands.

4. Hicken, N. F.; Best, R. R.; Hunt, H. B., and Harris, T. T.: The Roentgenological Visualization and Diagnosis of Breast Lesions by Means of Contrast Media, Am. J. Roentgenol. **39**:321-343, 1938.

CASE 2.—Miss A. M., 54 years of age, sought advice because of a "painful lump under her arm." Ten years previously the left breast had been removed because of "infected chronic cystic mastitis." Since that time she had always had

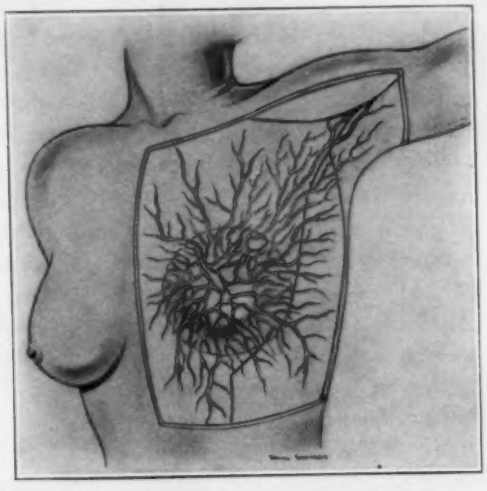

Fig. 3.—Composite schematic drawing representing the ramifications of the lactiferous ducts over the anterolateral chest wall. Note the axillary, subpectoral, midsternal and epigastric extensions. These were all seen by mammographic studies.

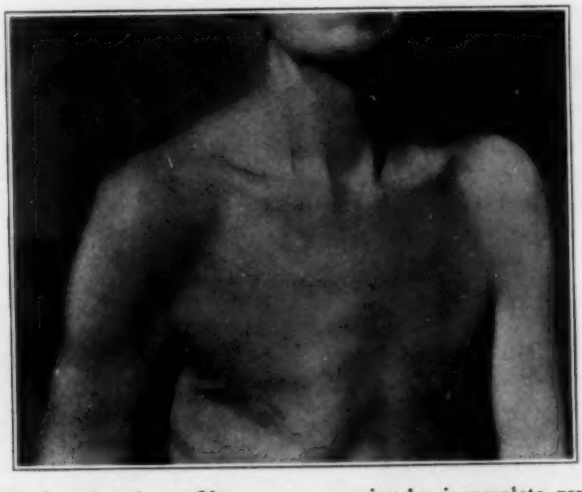

Fig. 4.—Patient in whom, fifteen years previously, incomplete removal of the right breast had been done for "chronic cystic mastitis." Adenocarcinoma developed in the residual mammary tissue.

a sense of discomfort in the left axillary region. During the past three months the tumor mass had rapidly increased in size and had become tender and painful. Exploration demonstrated the neoplasm to be composed of mammary tissue which

contained several small distended cysts. From the thick, tenacious cystic fluid pure cultures of streptococci were obtained.

It is obvious that in each of these cases the axillary segment of the breast was overlooked during the primary mastectomy, and the residual tissue underwent pathologic change. Complete mastectomies would certainly have prevented these catastrophes.

TECHNIC

As a result of these studies, it was learned that a complete mastectomy can be performed if certain points are observed. The following plan has been effective.

The entire mammary gland and axilla are prepared as for a radical amputation of the breast. The nipple is thoroughly cleansed of all incrustations, and inspissated plugs of debris are gently expressed from the orifices of the lactiferous ducts. Two of the patent estuaries in each quadrant of the nipple are cannulized and injected with a solution of methylene blue. The dye accurately outlines the ramifications of the mammary tissue. If the ducts are inadvertently incised during the operation, the escaping dye affords an excellent visual warning that incision is still within the confines of the mammary gland. If the surgeon keeps beyond the "blue zone" a complete mastectomy is assured.

The practice of amputating the breast through a small incision accounts for the incompleteness of most mastectomies. Such conservatism is prompted by a desire to give the patient a small, invisible scar. The transverse cutaneous incision usually fails to give adequate exposure of the axilla, and if the incision is carried far enough medially to expose the sternum and epigastric notch the scar is plainly visible when low-necked dresses are worn. These disadvantages have been overcome by the use of an oblique incision (fig. 5). The outer margin of the incision begins 1 inch (2.5 cm.) below the floor of the axilla and extends downward and medially toward the epigastric notch.

Extreme care is essential in reflecting the skin flaps, for adequate exposure is desirable. Usually the course of the cutaneous vessels has been previously outlined by transillumination studies, so that they will not be injured and viability of the flaps will be assured. The dissection is carried along in the subcutaneous zone close to the skin, so as not to leave any mammary tissue. The larger lactiferous ducts and their fine ramifications are clearly visualized by their methylene blue content; hence their integrity is preserved. It is surprising to learn that the skin flaps must be practically devoid of subcutaneous tissue if one desires to avoid the matrix of the breast.

It is imperative that the skin flaps be reflected so as to expose the axilla, the sternum, the epigastric notch and the anterior border of the

latissimus dorsi muscle. The wide denudation affords complete access to all segments of the breast, and one is surprised to find its ramifications so extensive.

Beginning beyond the "blue zone," at the midsternal line, the breast is carefully reflected (fig. 5 *B*) from the fascial covering of the pectoral muscles. (On two occasions the "blue colored milk ducts" have been seen to penetrate this pectoral fascia and enter the muscular substance.[5]

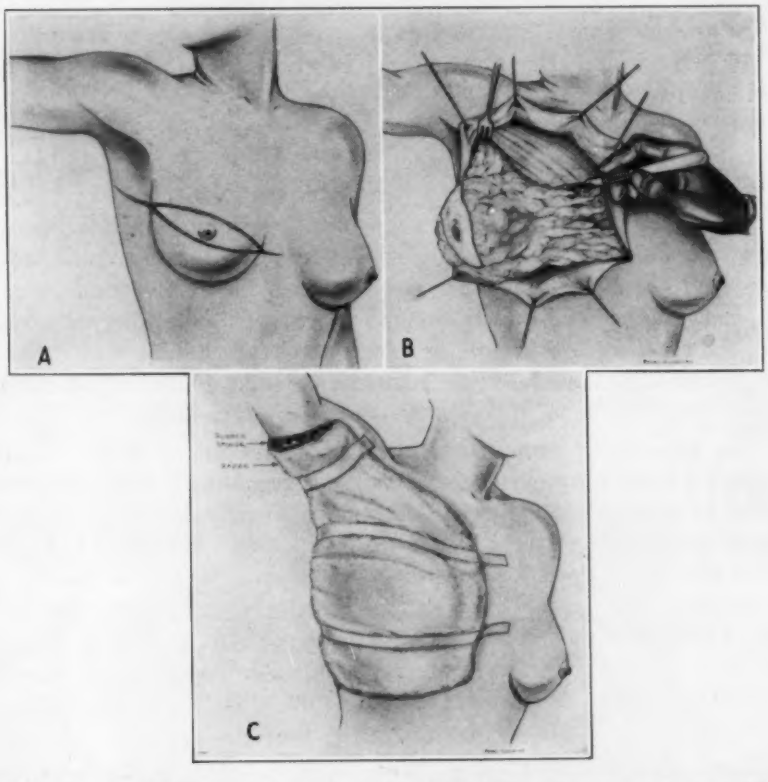

Fig. 5.—*A*, oblique mastectomy incision which gives adequate exposure without leaving scars that will show. *B*, manner of dissecting the breast from the pectoral fascia. Note the axillary and epigastric extensions of mammary and adipose tissue. *C*, compressive rubber sponge dressings employed to keep the skin flaps in intimate contact with their nutritional bed.

In these cases the fascia and penetrating lacteals were excised.) Care should be exercised to remove all mammary tissues from the epigastric space and along the lateral wall of the chest As the mobilized breast is

5. Wainwright, J. M.: Carcinoma of the Male Breast, Ann. Surg. **14**:837-859, 1927.

pulled upward and outward, its axillary segment can be easily followed and removed. Occasionally some of the matrix will extend between the two pectoral muscles, in which event it should be extirpated. Invariably the axillary segment extends well into the axilla. In some instances it has been necessary to dissect the dye-stained lactiferous ducts from the axillary vein, but as a rule they do not extend so far. If the axilla is not entered, one is almost certain to overlook mammary tissue. Complete removal of the mammary gland leaves a large area of traumatized tissue which of necessity will produce serum. If the serous effusions are permitted to accumulate, they separate the skin flaps from their nutritional bed and favor sloughing. Dependent counterdrainage overcomes such danger. I have found that compressive rubber sponge dressings not only minimize postoperative hemorrhages and serous effusions but hold the skin flaps in firm apposition to the wall of the chest, thus favoring rapid restoration of their nutrition. These large sponges cover the entire operative area and are held securely in place by adhesive strapping (fig. 5 *C*). If they are applied too tightly, the pressure obliterates the cutaneous vessels and favors necrosis of the skin; if too loosely, they permit serum to collect. Experience soon teaches the proper application.

During the first twenty-four hours the arm should be abducted to an angle of about 90 degrees. This tends to stretch the pectoralis major muscle so that when the skin becomes adherent to it free and painless motion will result. Several times during the day the arm may be placed against the wall of the chest and gentle passive exercises given. This minimizes muscular fatigue and assures early restoration of function.

SUMMARY

Contrast mammographic studies of 385 breasts indicate that the lactiferous ducts spread over the entire anterolateral wall of the chest. In 95 per cent of the mammograms the ducts passed up into the axillary fossa; in 15 per cent they were seen to extend downward into the epigastric space; in 2 per cent they coursed along the lateral wall of the chest beyond the limits of the anterior border of the latissimus dorsi muscle, and in 2 instances they passed across the midsternal line to the opposite side. In no instance was there an anastomotic communication between the two breasts.

A simple mastectomy should aim to remove the entire mammary gland. Unfortunately, this is seldom accomplished. The lactiferous ducts of 17 breasts which had been removed by "routine mastectomy" were injected with a solution of methylene blue. Wherever the breast tissue had been incompletely removed, the dye escaped from the severed ducts. It was found that in 94 per cent of cases mammary tissue had been left attached to the reflected skin flaps: in 88 per cent the axillary

appendage of the breast had been incompletely excised; in 23 per cent the sternal extensions had been severed, and in 11 per cent the epigastric ramifications had been left behind. In 75 per cent of all the cases studied there were multiple areas of incomplete removal.

A technic is described which assures complete removal of the mammary gland. This includes preoperative injections of methylene blue into the lactiferous ducts and operation with the incision kept well beyond the "blue zone."

Compressive sponge dressings minimize the hazards of postoperative hemorrhage and serous effusion and hold the skin flaps in intimate contact with their nutritional bed.

Residual mammary tissue may undergo either normal involution or neoplastic change. Cases are reported in which adenocarcinoma and chronic cystic mastitis developed in residual mammary tissue in patients who years previously had been subjected to "mastectomy."

508 Medical Arts Building.

INFECTION AS A CAUSE OF MASSIVE HEMORRHAGE IN CHRONIC PEPTIC ULCER

REPORT OF FIVE CASES

JAMES R. LISA, M.D.
AND
DAVID S. LIKELY, M.D.
NEW YORK

This communication is a report of 5 cases of death from hemorrhage due to infection in chronic gastric and duodenal ulcers. They were among the last 7 cases of exsanguinating hemorrhage from ulcer observed in the past seven and one-half years at the New York City Hospital, Welfare Island. In each of the 5 cases the criteria of chronicity were answered—distortion of the architectural pattern of the wall, fibrosis of the base of the ulcer and some degree of chronic inflammatory cellular reaction. In all cases bacteria were demonstrated in the sections at the point of hemorrhage. Clinical evidence in some of the cases proved the presence of septicemia.

REPORT OF CASES

CASE 1.—A white man 71 years old was admitted to the surgical division of the City Hospital, service of Dr. A. S. Morrow, on May 29, 1932, in profound shock. He gave a history of vomiting a large amount of blood the previous evening and of a tarry stool. The only other significant symptom was epigastric pain, which had been present for the past four years. There had never been a previous hemorrhage.

He appeared almost exsanguinated. He complained of thirst. The blood pressure was low and the temperature subnormal. Tachycardia was observed. The value for hemoglobin was 35 per cent. With sedatives and a transfusion he improved slightly; then hemorrhage recurred, and death ensued twelve hours after admission.

Necropsy.—On the posterior wall of the first portion of the duodenum was a chronic ulcer measuring 5 cm. in diameter. In the center was an eroded vessel. The small and large intestines were filled with partially clotted blood.

Histologic Examination.—The ulcer was chronic; the base was replaced by dense scar tissue covered by a thin necrotic membrane. The artery was thick and sclerotic; its wall was involved by necrosis. The lumen of the artery throughout its extent contained gram-negative bacilli and gram-positive cocci (fig. 1).

From the Pathologic Laboratory and the First Medical Division of the City Hospital.

Pathologic Diagnoses.—The pathologic diagnoses were chronic duodenal ulcer with erosion of the artery from infection and exsanguinating hemorrhage.

CASE 2.—A white man 47 years of age was admitted to the second medical division of the City Hospital, service of Dr. John McCabe, on Dec. 31, 1934. For four days he had complained of nausea, vomiting and pains in the chest, abdomen and back. These symptoms had occurred during a drinking bout. They

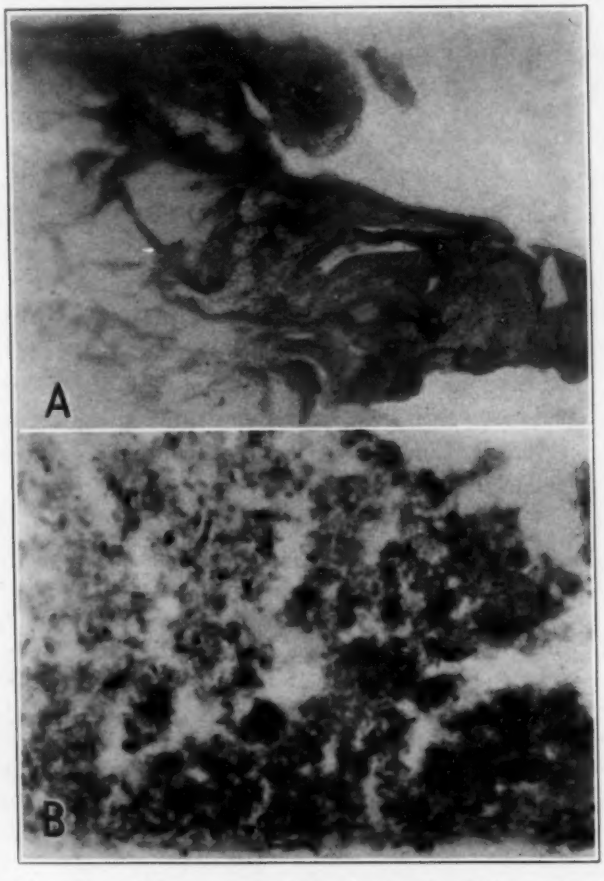

Fig. 1 (case 1).—*A*, low power photomicrograph of the ulcer, showing the course of the artery and the point of rupture. *B*, bacilli and cocci found throughout the course of the artery (Gram's stain).

had been accompanied with nausea and vomiting and followed by chills, fever and pain. The patient was chronically alcoholic. The other data were irrelevant.

He was acutely ill. The temperature was 102 F., the pulse rate 130 and the respiratory rate 28. There were signs of pneumonic consolidation of the left lung. The sputum was bloody. The liver was large and tender. Culture of the blood revealed Friedländer's bacillus.

The course remained typically pneumonic until the fifth day, when the patient suddenly raised about 12 ounces (360 cc.) of fresh blood. He became very apprehensive, and the pulse became almost imperceptible. Death followed in two and one-half hours.

Necropsy.—The stomach contained about 1 liter of partially clotted blood. There were seven chronic ulcers. The largest was on the posterior wall, just below the esophageal orifice. It measured 3 by 5 cm. and had a large eroded artery in the base. Two smaller ulcers involved the posterior wall, close to the lesser

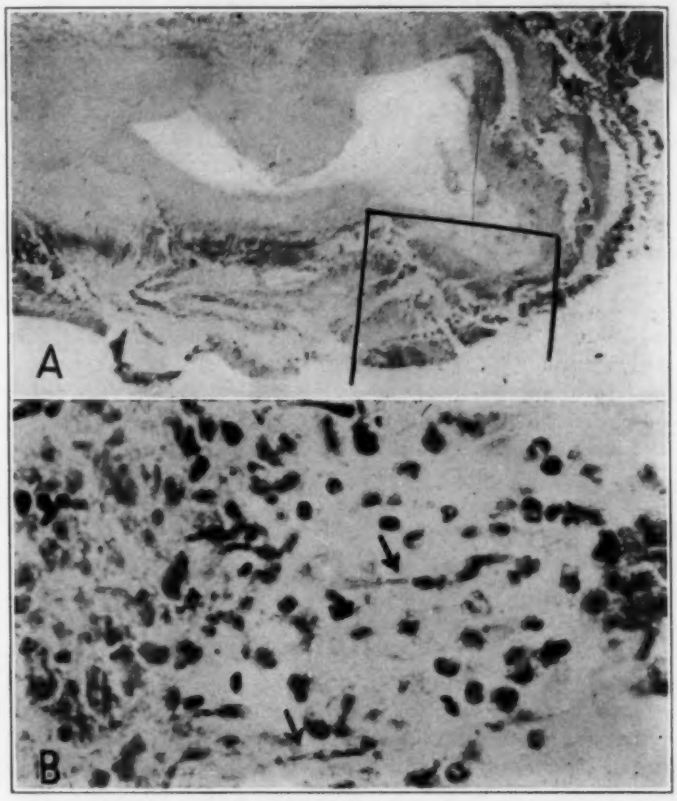

Fig. 2 (case 2).—*A*, acute infectious aneurysm of the artery in the base of the ulcer. *B*, bacilli in the region marked in the first photomicrograph (Gram's stain).

curvature. Four smaller ulcers were prepyloric. The small intestines and the cecum were filled with fresh blood. The contents of the large intestine were tarry.

Histologic Examination.—The histologic appearance of the largest ulcer only is described. The large artery showed an acute necrotic lesion containing many polynuclear cells and destroying the entire thickness of the wall. Within this necrotic zone were numerous gram-negative encapsulated bacilli morphologically similar to Friedländer's bacillus (fig. 2).

Pathologic Diagnoses.—The pathologic diagnoses were: pneumonia due to Friedländer's bacillus, with septicemia and acute pericarditis; multiple chronic gastric ulcers; acute infectious aneurysm of a branch of the gastric artery in the chronic ulcer, with rupture and exsanguinating hemorrhage; chronic gastritis; syphilis of the aorta, and chronic prostatitis.

CASE 3.—A white man 53 years old was admitted to the second medical division of the City Hospital, service of Dr. B. F. Donaldson, on Feb. 17, 1938, because of weakness, anorexia, loss of weight and diarrhea, all of three weeks' duration. In the past half year he had lost 25 pounds (11.3 Kg.) in weight.

He was emaciated and very anemic. Physical examination showed little abnormality. The apex of the left lung revealed wheezing expiration. The blood pressure was 72 systolic and 50 diastolic. The abdomen was somewhat spastic, and palpation was unsatisfactory. The temperature was 100.6 F., the pulse rate 80 and the respiratory rate 24. The value for hemoglobin was 40 per cent. There were 2,500,000 erythrocytes per cubic millimeter of blood. The urine was normal. Electrocardiographic tracings were normal. Chemical study of the blood revealed no abnormality. The Wassermann reaction was negative. A roentgenogram of the chest was normal. The stool consistently gave a positive reaction for blood.

For one month the patient had a fever of unknown origin, with daily fluctuations of temperature between 99 and 102 F. The anemia and weakness increased in spite of all measures. One month after admission he had a severe chill and the temperature rose to 105 F. Culture of the blood revealed hemolytic streptococci. Under administration of prontosil (the disodium salt of 4-sulfamidophenyl-2'-azo-7'acetylamino-1'-hydroxynaphthalene-3',6'-disulfonic acid) the temperature gradually fell, but the general condition appeared worse. Repeated cultures of the blood showed decreasing numbers of organisms but never became sterile. Pallor and weakness continued to increase, and death occurred on April 15.

Necropsy.—The stomach contained massive blood clots. On the lesser curvature, 8 cm. from the pylorus, was a chronic ulcer 3 cm. in diameter with a nest of petechial hemorrhages near the proximal edge. The right psoas muscle was replaced by a tuberculous abscess cavity containing greenish pus from which a hemolytic streptococcus was isolated on culture.

Histologic Examination.—Buried in the granulation tissue of the ulcer in the region of the petechial hemorrhages were masses of gram-positive streptococci, filling many of the capillaries. The surface of this region was covered by fibrin containing a few organisms (fig. 3).

Pathologic Diagnoses.—The pathologic diagnoses were chronic gastric ulcer with acute streptococcic infection and massive hemorrhage and chronic tuberculous abscess of the psoas muscle with hemolytic streptococcus infection.

CASE 4.—A white man 76 years of age was admitted to the second medical division of the City Hospital, service of Dr. J. H. Cudmore, on March 26, 1939, because of black vomitus, loss of weight, tarry stools and edema of the ankles, present for five years. He was pale and undernourished. On examination there were pitting edema of the ankles, tachycardia, a normal temperature and normal respirations. Examination otherwise gave essentially negative results. Early the next morning he vomited a large amount of fluid and clotted blood. Two and one-half hours later there was a second attack, and he died within thirty minutes.

Necropsy.—The stomach was filled with fluid and clotted blood. A large chronic ulcer encircled the pylorus. The border was firm and raised. The base was formed by the head of the pancreas. In the upper portion of the ulcer was an eroded vessel.

Histologic Examination.—Section through the region of the eroded ulcer showed simple chronic ulcer with complete destruction of the muscular wall and replacement by scar tissue. The eroded, sclerotic vessel lay at right angles to the surface. In the region of the rupture there was an acute inflammatory process involving the arterial wall and containing gram-positive cocci in clumps, suggestive of staphylococci (fig. 4).

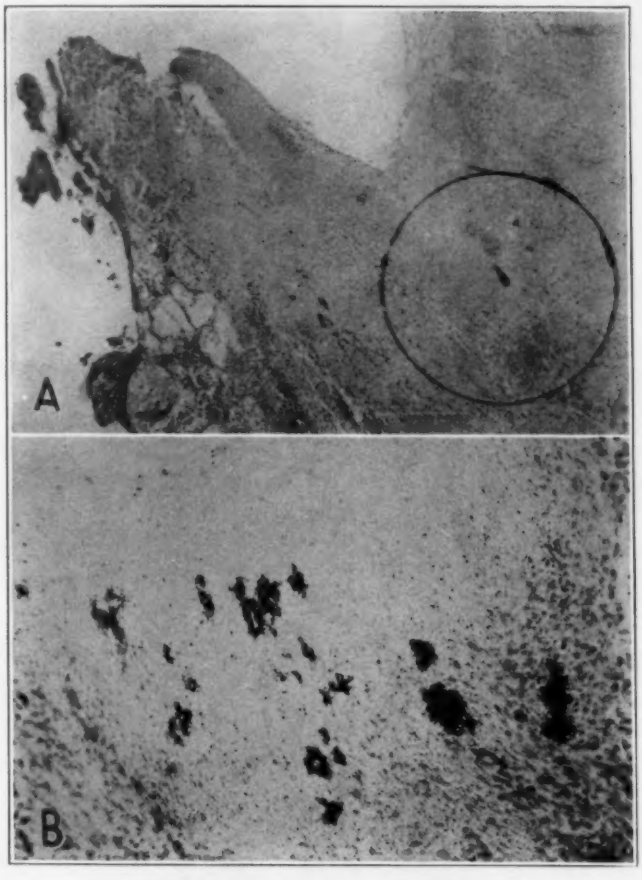

Fig. 3 (case 3).—*A*, angle of the ulcer, with organisms buried in the granulation tissue. *B*, bacteria in the capillaries (Gram's stain).

Sections taken at a distance from the point of hemorrhage showed malignant transformation of the epithelium; the architectural pattern of chronic ulcer was preserved.

Pathologic Diagnoses.—The pathologic diagnoses were: chronic pyloric ulcer with carcinomatous degeneration; acute infectious inflammation with erosion of the artery, and exsanguinating hemorrhage in the nonmalignant portion of the ulcer.

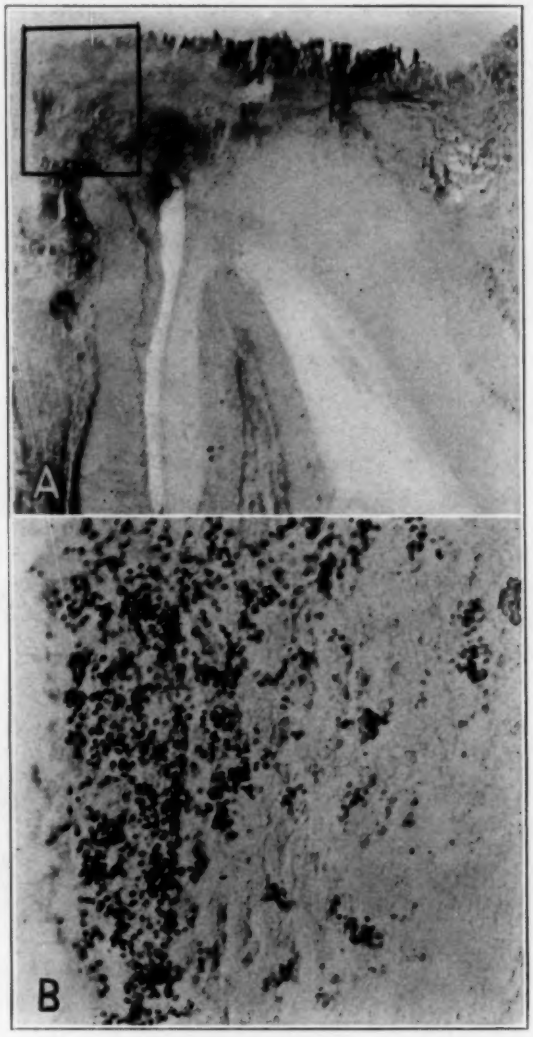

Fig. 4 (case 4).—*A*, acute infectious aneurysm of the artery in the base of in ulcer. *B*, organisms seen in the region outlined in *A* (Gram's stain).

CASE 5.—A white man apparently beyond the stated age of 56 was brought to the City Hospital after he had collapsed in the street. He was admitted to the surgical division, service of Dr. Frederick Bancroft, on March 24, 1939. Three months previously a right inguinal hernia had developed. For ten days the patient

had not eaten well because of loss of appetite; for seven days there had been no bowel movements, and for three days the hernia had been irreducible and painful and there had been vomiting. Operation was performed, and healing was normal. For a few days the temperature was slightly raised, and the patient became irrational and psychotic. Later he had sacral bed sores and appeared seriously ill, but no definite signs could be elicited to account for his general condition. On April 13, nineteen days after the operation, he vomited a large amount of blood and died suddenly.

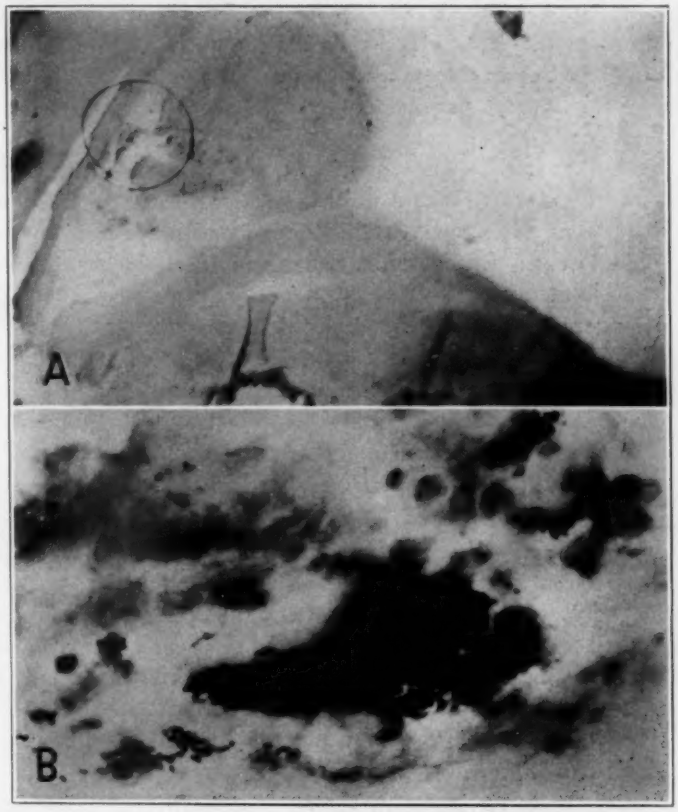

Fig. 5 (case 5).—*A*, low power photomicrograph of the large open point of rupture. *B*, organisms observed in the masses of fibrin within the lumen of the vessel (Gram's stain).

Necropsy.—The operative wound was healed. Clotted blood was present in the stomach and intestines. In the first portion of the duodenum, on the posterior wall, was a chronic ulcer measuring 3 by 2 by 2 cm., the base formed by the head of the pancreas. The surface was covered by an adherent blood clot which on removal revealed an eroded pancreaticoduodenal artery.

Histologic Examination.—The tip of the eroded artery at the surface of the ulcer was involved in an acute necrotic process. Within the lumen of the vessel

and fairly deep in the course were masses of fibrin and numerous gram-positive organisms in clumps and chains (fig. 5).

Pathologic Diagnoses.—The pathologic diagnoses were chronic duodenal ulcer; acute infectious arterial aneurysm of the ulcer with rupture and exsanguinating hemorrhage; decubital ulcers of the sacrum, and hydronephrosis on the left with stones.

COMMENT

Massive hemorrhage from chronic ulcer of the stomach or of the duodenum is one of the most serious accidents which can occur. In many instances its etiology is obscure. Crohn and Shwartzman [1] concluded that it is due to a local Shwartzman phenomenon from infections of other regions and particularly from acute diseases of the upper respiratory tract. They stated that in their opinion infection does not occur in the ulcer itself. The demonstration of bacteria has been reported occasionally in cases of acute ulcer in which death followed massive hemorrhage. Hartung and Warkany [2] reported the case of a 6 year old boy who died of hemorrhage from a duodenal ulcer during the course of meningococcic meningitis. Among other organisms seen in the base of the ulcer were gram-negative diplococci morphologically resembling Neisseria. In the series of causes of acute ulcer in children reported by Gerdine and Helmholtz [3] there were several cases of hemorrhage in which bacteria were demonstrable. Sanford, Hughes and Weems [4] reported an acute ulcer with hemorrhage and pneumococci in a case of pneumonia.

The seasonal incidence of recurrence of symptoms and of hemorrhages in ulcer is a well recognized phenomenon. Crohn and Shwartzman reported that an unusual number of patients having ulcers with hemorrhage were admitted to the Mount Sinai Hospital, New York, in February and March 1937, during a period of severe grippal infections. They stated that the same experience was encountered at Queens General Hospital, New York, at the same time. In the present series, 4 of the cases were observed in the winter months (December, February and March) and 1 in the spring (May).

The bacterial causative factor varied in the different cases, although the streptococcus was the most frequent organism. From antemortem

1. Crohn, B. B., and Shwartzman, G.: Ulcer Recurrences Attributed to Upper Respiratory Tract Infection: A Possible Illustration of the Shwartzman Phenomenon, Am. J. Digest. Dis. & Nutrition **4**:705, 1938.

2. Hartung, C. A., and Warkany, J.: Duodenal Ulcer as a Cause of Death in Meningococcal Meningitis, J. A. M. A. **110**:1101 (April 2) 1938.

3. Gerdine, L., and Helmholtz, H. F.: Duodenal Ulcer in Infancy: An Infectious Disease, Am. J. Dis. Child. **10**:397 (Dec.) 1915.

4. Sanford, C. H.; Hughes, J. D., and Weems, J.: Pneumonia Complicated by Acute Pneumococcic Hemorrhagic Ulcerative Gastroenteritis (Dieulafoy's Erosion): Report of Two Cases, Arch. Int. Med. **62**:597 (Oct.) 1938.

cultures of the blood, Friedländer's bacillus and hemolytic streptococci were isolated, and organisms of corresponding morphologic character were demonstrated at the point of hemorrhage. The other organisms observed could be judged only on the morphologic appearance. One was a definite chain coccus; another was of the streptococcus-pneumococcus group, and the third resembled a staphylococcus.

In most of the cases in our series the source of the infection was difficult to determine precisely. Only in case 2 was it clearly evident that the pneumonic process was the basis. The abscess with hemolytic streptococci found in the psoas muscle in case 3 seemed an unlikely source. It is more probable that septicemia from some other focus localized in two areas of previous damage, the abscess and the ulcer. In case 5 the decubital ulcer was the probable focus; the diseased kidney was a possible one, but its condition was "end stage" rather than active. In the other 2 cases the sources were entirely obscure.

The findings in this series offer a striking parallel to the production of acute ulcers by bacteria. Gerdine and Helmholtz [3] stressed the bacterial origin of ulcer, particularly in children. Harkins [5] showed that infected burns are prone to ulcerate and cited several observers who related sepsis and ulcer. We can draw no conclusion from our series in regard to the etiology of ulcer, but it seems reasonable to believe that in the presence of a transient bacteremia a chronic ulcer offers a favorable site for the localization of organisms and the production of an infectious process leading to rupture of vessels with resulting severe hemorrhage. They also suggest another avenue of preventive therapy in cases of recurrent hemorrhage, i. e., the search for and eradication of foci of chronic infection.

SUMMARY AND CONCLUSIONS

Five cases of chronic gastric and duodenal ulcer with death from exsanguinating hemorrhage are reported. A bacterial cause for the hemorrhage was demonstrated in each case. Cultures of blood in 2 cases yielded bacteria. The source of infection in 1 instance was the lung; in the others it was obscure. The suggestion is advanced that eradication of foci of chronic infection may be a preventive measure of value in cases of recurrent hemorrhage in chronic ulcer.

5. Harkins, H. N.: Acute Ulcer of Duodenum (Curling's Ulcer) as Complication of Burns: Relation to Sepsis; Report of Case with Study of One Hundred and Seven Cases Collected from the Literature, Ninety-Four with Necropsy, Thirteen with Recovery; Experimental Studies, Surgery **3**:608, 1938.

CEREBRAL COMPLICATIONS FOLLOWING SURGICAL OPERATION

I. ETIOLOGY AND PATHOLOGY

ALBERT BEHREND, M.D.
AND
HELENA E. RIGGS, M.D.
PHILADELPHIA

Postoperative complications of many types have long commanded the respectful attention of surgeons. Among the most serious, and the least well understood, are those which affect the central nervous system. Motor paralyses occurring in persons of the older age groups after operations have long been considered a coincidental accident having no direct connection with the operation. Such complications in younger persons have usually been looked on as the result of embolism from the operative site. Sudden death during or immediately after operation has been ascribed to cerebral embolism or to individual idiosyncrasy to the anesthetic. Prolonged coma, convulsions or psychic disturbances occurring during or shortly after operation have been commonly considered the result of the toxic effects of the anesthetic or of the "toxemia" arising from the condition requiring operation.

In this paper we wish to show that the cerebral complications of various types encountered after surgical operation may be the result of cerebral anoxia resulting from acute general circulatory collapse precipitated by the administration of an anesthetic, plus the trauma of operation, in persons whose margin of circulatory reserve has been reduced by a masked chronic circulatory insufficiency.

Our investigations indicate that so-called postoperative cerebral embolism is extremely uncommon. Cerebral complications are encountered, however, even in the best regulated clinics,[1] and we are able to show that in a large city hospital they are not rare. One of us (H. E. R.) has had the opportunity to examine the brain and viscera in 21 cases in which the patients died after operation at the Philadelphia General Hospital. In each case symptoms referable to the cerebrum complicated the postoperative course.

From the Department of Thoracic Surgery and the Laboratory of Neuropathology, Philadelphia General Hospital.

Read before the Section on Surgery, General and Abdominal, at the Ninetieth Annual Session of the American Medical Association, St. Louis, May 17, 1939.

1. Woltman, H. W.: Postoperative Neurologic Complications, in Collected Papers of the Mayo Clinic and the Mayo Foundation, Philadelphia, W. B. Saunders Company, 1937, vol. 29, pp. 712-722.

TYPE OF MATERIAL

The 21 cases comprising material for this study came from the several surgical services of a large city hospital. Preoperatively only 6 patients (28 per cent) could be considered poor surgical or anesthetic risks. There were 4 midthigh amputations for gangrene, a splenectomy for hemolytic anemia and an exploratory laparotomy for intestinal obstruction.

The average age of the 21 patients was 38 years, and only 4 patients (19 per cent) were over 50 years of age (fig. 1).

The operations included celiotomy (12 cases) operations on the femur (5 cases), obstetric anesthesia (2 cases), dilatation and evacuation of the uterus (1 case) and incision of a paronychia (1 case).

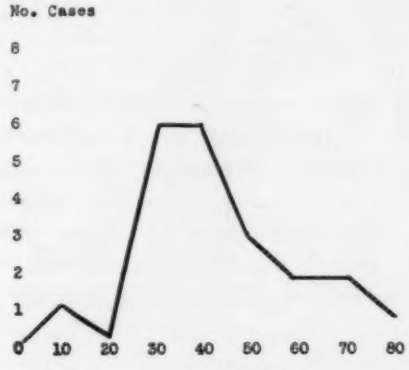

Fig. 1.—Age incidence of postoperative cerebral complications (21 cases).

The anesthetics used were as follows: ether, 12 cases; cyclopropane, 4 cases; nitrogen monoxide, 3 cases, and procaine hydrochloride, for spinal anesthesia, 2 cases.

SYMPTOMS

The very diversity of symptoms heretofore noted by other observers is a strong argument against the theory of cerebral vascular accident. In our series of 21 cases the symptoms were usually those suggesting diffuse involvement of the entire brain, and, as a rule, at some period more than one symptom was present in each case.

The following symptoms of cerebral dysfunction were noted in our series:

Death during operation	3 cases
Psychic disturbances	3 cases
Prolonged coma (twelve to twenty-four hours)	5 cases
Generalized convulsions	5 cases
Focal cerebral symptoms (paralyses)	5 cases

Four patients with focal cerebral symptoms were under 33 years of age. The fifth, aged 61, had shown transient weakness of the right side of the body for nine days prior to operation, complete paralysis developing within twenty-four hours after operation.

Convulsions and prolonged coma may be observed while the patient is in the operating room. Psychotic manifestations may become apparent within a few hours after consciousness returns or may be noticed after several days. In 2 cases (not included in this series) we have observed psychoses which developed within forty-eight hours of operation to disappear completely, only to be followed by hemiplegia on the fifth postoperative day in 1 case and on the seventh in another. Both the patients died. Fourteen (76 per cent) of the patients in our series surviving longer than twelve hours died with hyperpyrexia unexplainable on an infectious basis.

ETIOLOGY AND PATHOLOGY

Ornsteen [2] has briefly reviewed the controversy over the origin of postoperative focal cerebral symptoms which occurred during the latter half of the last century. His report shows that neurologists and pathologists had to devise various ingenious routes to carry thrombi from the major venous circulation to the cerebral arterial system. While it is probable that in a few postoperative cerebral accidents the cause may be found to be embolism, thrombosis affecting the end arteries or cerebral hemorrhage, evidence is accumulating which indicates that another factor is more often involved.

Recently, Courville [3] has made the important suggestion that anoxia may account for the clinical and pathologic picture in cases of postoperative cerebral involvement. Since in all his cases [4] nitrogen monoxide was the anesthetic, he felt that there was a direct relation between the asphyxia associated with this anesthetic and the cerebral anoxemia. He concluded that the anoxemia must result from a sudden circulatory or respiratory failure during the anesthetic period or must be due to the effects of oxygen want incident to prolonged nitrogen monoxide anesthesia.

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2. Ornsteen, A. M.: Hemiplegia Following Childbirth and Pelvic Operations, Arch. Neurol. & Psychiat. **5**:353 (March) 1921.

3. Courville, C. B.: Asphyxia Following Nitrous Oxide Anesthesia, Medicine **15**:1129 (May) 1936; Pathogenesis of Necrosis of Cerebral Gray Matter Following Nitrous Oxide Anesthesia, Ann. Surg. **107**:371 (March) 1938.

4. Stewart, J. D., and Rourke, G. M.: Changes in Blood and Interstitial Fluid Resulting from Surgical Operation and Ether Anesthesia, J. Clin. Investigation **17**: 413 (July) 1938.

Gross inspection of the brain in our series lent no support to the theory of infarction as a result of embolism. Histologically [5] we were able to confirm Courville's theory of widespread cellular degeneration throughout the brain, regardless of the type of clinical manifestation of cerebral involvement. In every case there was generalized capillary damage with widespread parenchymatous degeneration due to pericellular and interstitial edema. Although the edema due to capillary damage was universal, the cellular degeneration was most marked in the association areas of the cortex, the sympathetic ganglions in the gray matter around the third and fourth ventricles and lenticular nucleus, the dentate and

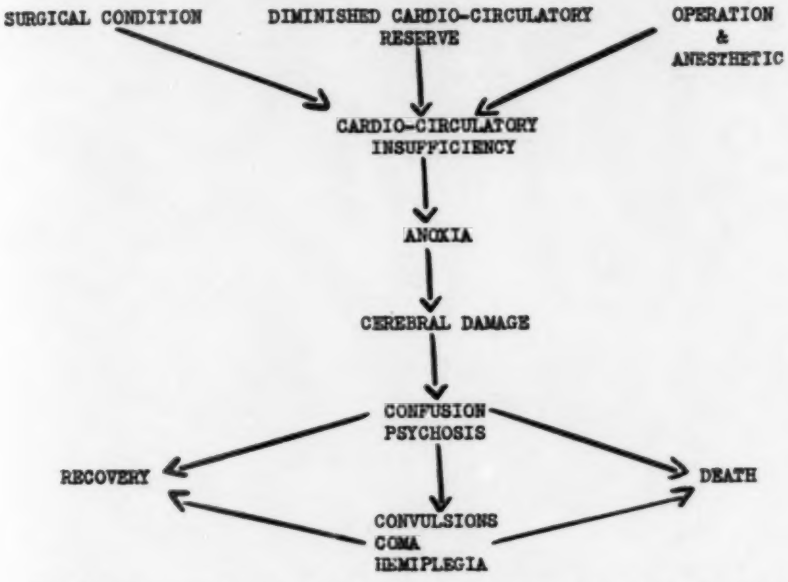

Fig. 2.—Pathogenesis and mechanism of postoperative cerebral complications.

Purkinje cells of the cerebellum and the region of the inferior olive in the medulla. Since these are the areas that Chornyak [6] has found most

5. The stain used on all sections is a trichrome stain developed by Miss Edna Beyer, technical assistant in neuropathology, laboratory of neuropathology, Philadelphia General Hospital. All forms of connective tissue and collagen stain blue; parenchymatous tissue and muscles stain red. In degenerative conditions muscles and parenchymatous cells are increasingly basophilic. By means of this stain it is possible to differentiate acute degenerative changes from those which are more chronic.

6. Chornyak, J.: Structural Changes Produced in the Human Brain by Oxygen Deprivation (Anoxemia) and Their Pathogenesis, Ann Arbor, Mich., Edwards Brothers, Inc., 1938.

severely affected in animals subjected to atmospheres deficient in oxygen, this would further suggest that Courville's theory of asphyxia as a factor in the production of cerebral symptoms after anesthesia might be extended to include not only nitrogen monoxide anesthesia but all forms of anesthesia.

Patients who survived less than forty-eight hours[7] showed no evidence of reaction indicating attempted repair. In 8 of the 10 patients

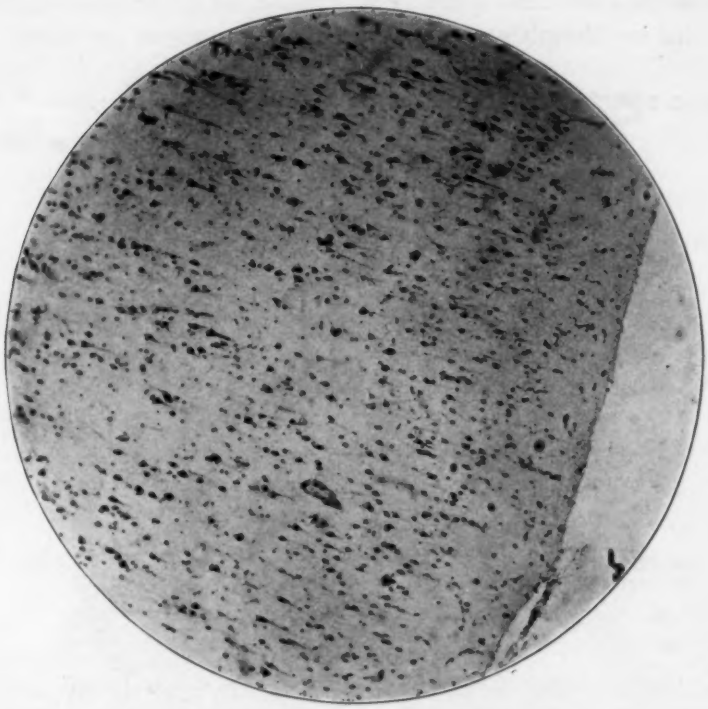

Fig. 3.—Section of the cerebral cortex (× 57, toluidine blue stain). The patient died within twelve hours after the operation. There were widespread degenerative changes in the ganglion cells. There was local loss of cells in layers 3 and 4 (Brodmann). Note the patent cortical arteriole.

who survived from two to nine days there were focal areas of glial and phagocytic activity, suggesting beginning repair and scar formation.

Only 2 patients had a history of sudden temporary cardiac or respiratory failure during operation. In none of our cases was the period of anesthesia unusually long. Operation was performed on 3

7. McAllister, F. F.: The Effect of Ether Anesthesia on the Volume of Plasma and Extracellular Fluid, Am. J. Physiol. **124**:391 (Nov.) 1938.

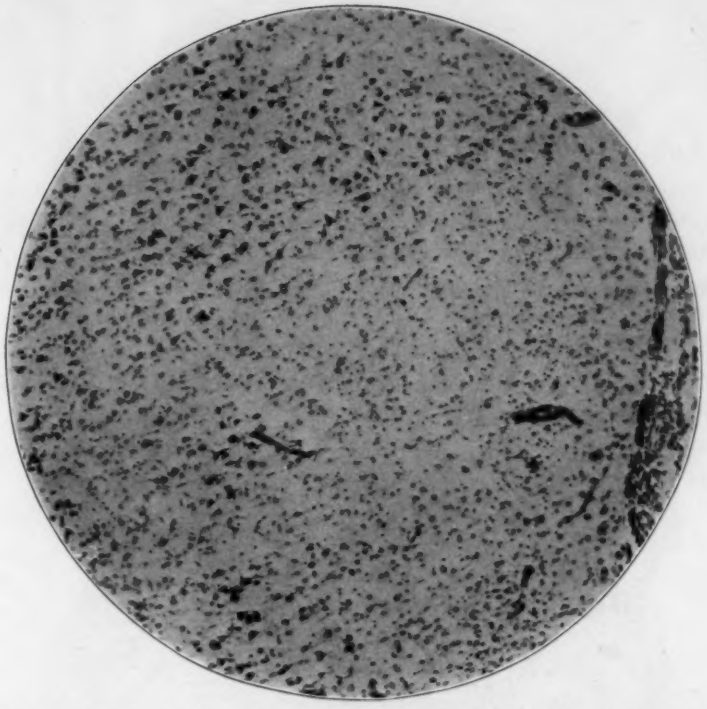

Fig. 4.—Section of the cerebral cortex (×57; toluidine blue stain). Delayed death occurred after a surgical operation. There was a focal area of loss of ganglion cells, with proliferation of astrocytes and microglia (necrobiosis). The remaining ganglion cells showed severe ischemic degeneration. Note the patent vessels with progressive alteration in their walls.

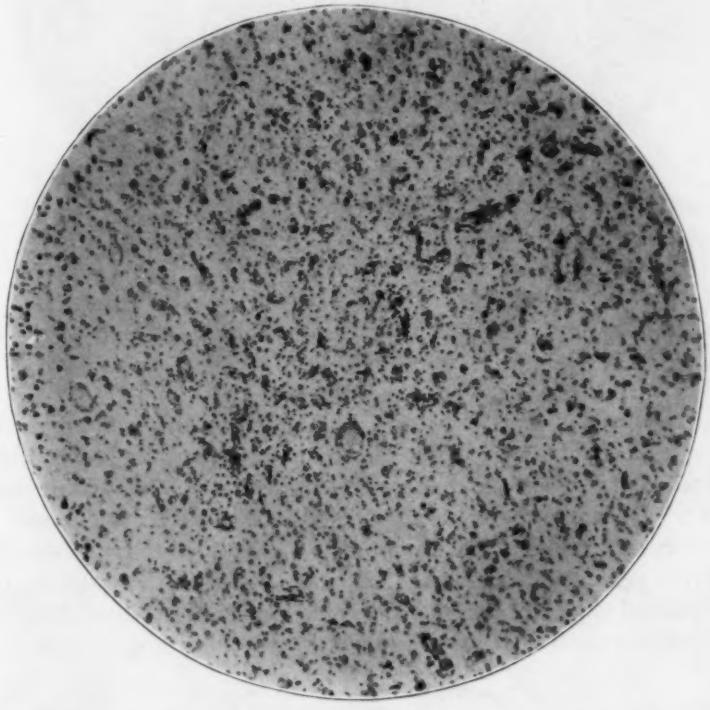

Fig. 5.—Section of the cerebral cortex (× 57; toluidine blue stain). Delayed death occurred after a surgical operation. There was total loss of ganglion cells, with proliferation of astrocytes and microglia. Note the patent blood vessels.

patients under light, brief nitrogen monoxide anesthesia, and in 2 cases inhalation anesthesia was not used, spinal anesthesia being substituted. In other words, it was observed that cerebral symptoms might follow the use of any type of anesthetic agent and were not related to the duration of anesthesia or to accidents occurring during the period of anesthesia. This suggested that we were dealing with some factor contributing to cerebral anoxia which was unrelated to the surgical status or to the anesthetic itself.

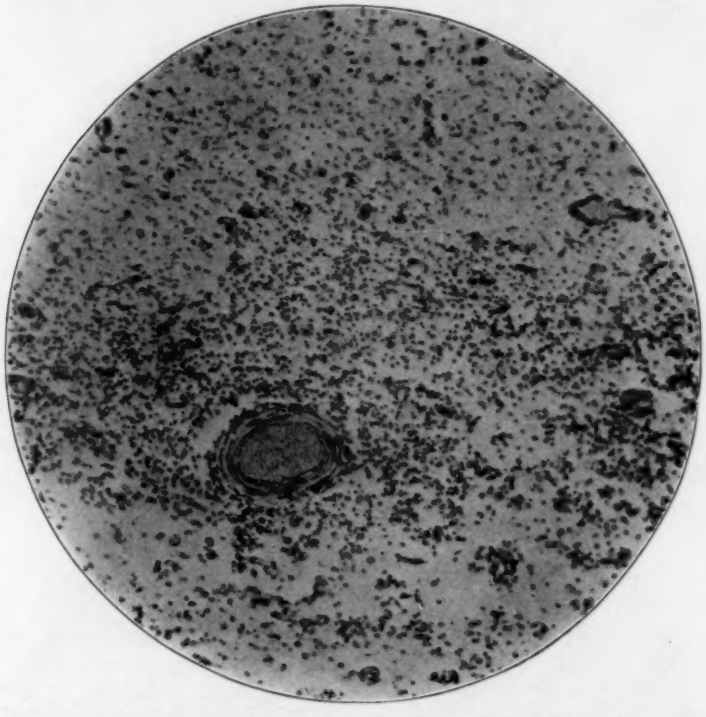

Fig. 6.—Section of the cerebral cortex (× 57; toluidine blue stain). Delayed death occurred after a surgical operation. Note the local area of encephalomalacia. Masses of phagocytic cells surrounded the patent artery.

In view of the fact that edema and congestion not only of the brain but of the viscera were observed at autopsy, it would seem that the cerebral degeneration is more reasonably attributable to the combined effect of anesthesia and operation on general circulatory efficiency with secondary reflection in the brain than to a direct selective anoxia of the brain cells alone. The predominance of cerebral symptoms might be explained clinically by the fact that evidence of cerebral dysfunction is frequently so dramatic as to obscure the accompanying signs of dis-

Fig. 7.—Section of the medulla in the region of the inferior olive (× 69; trichrome stain). Death occurred during tonsillectomy. The patient was a child aged 9 years. Note the thickening and hyalinization of the walls of the blood vessel, which, with the perivascular degeneration, suggests cerebral circulatory insufficiency antedating the period of anesthesia.

Fig. 8.—Section of the heart muscle (× 69; trichrome stain). Death occurred during an operation performed with the patient under obstetric anesthesia. The age of the patient was 27. There were intense dilatation and stasis in the venous radicles. Edema of the tissue was present. There was increase of interstitial connective tissue, suggesting preexisting circulatory stasis.

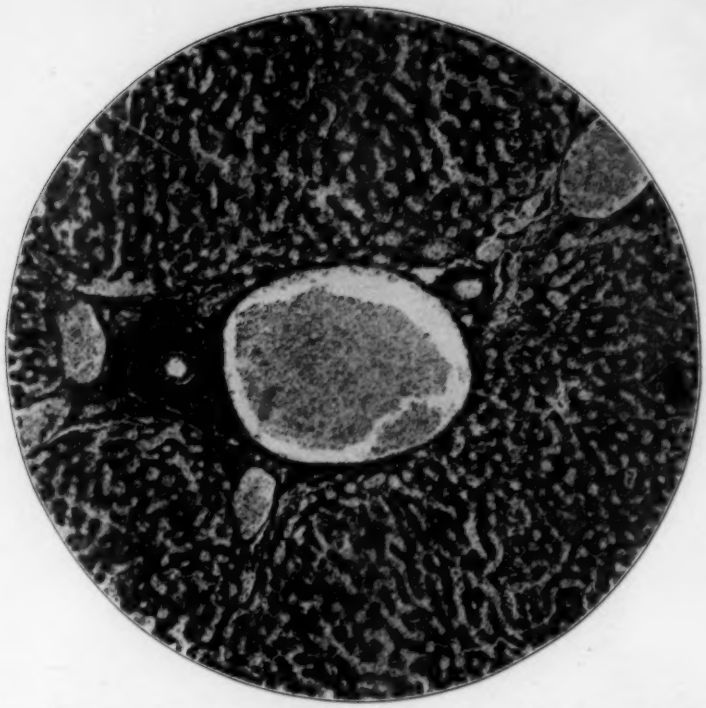

Fig. 9.—Section of the liver (× 69; trichrome stain). Death occurred during an operation performed with the patient under obstetric anesthesia. The age of the patient was 21. There was acute stasis indicated by hepatic sinusoids packed with red cells. Note the increase of connective tissue around the bile duct, indicating preexisting circulatory insufficiency.

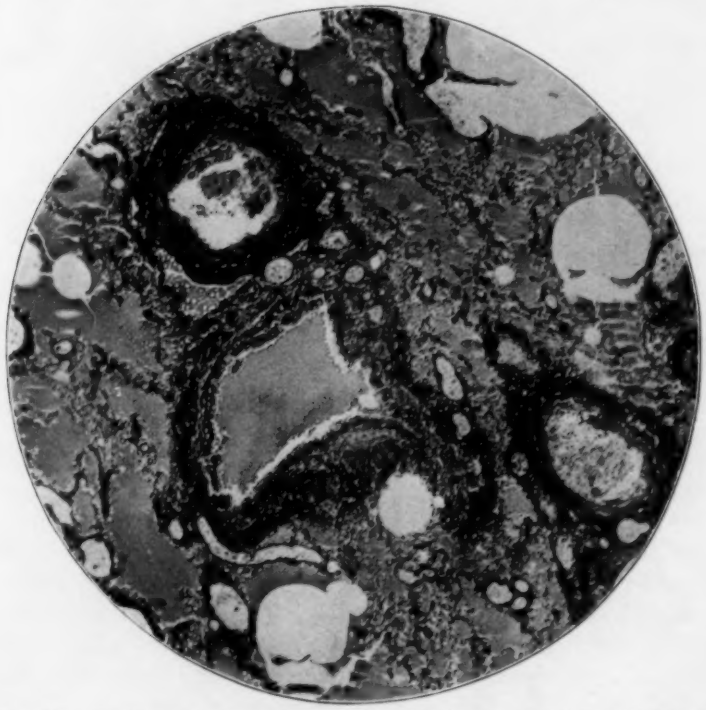

Fig. 10.—Section of the lung (× 69; trichrome stain). Death occurred during an operation performed with the use of spinal anesthesia. The age of the patient was 33. There was pulmonary edema as evidence of acute stasis. Perivascular fibrosis was present, suggesting preexisting circulatory insufficiency.

orders of visceral function. Physiologically, the effect of general circulatory insufficiency is most evident in the brain because of the effect of the closed box of the skull on the increased volume of the brain (due to circulatory stasis) and because of the high metabolic rate and oxygen requirements of cerebral tissue.

ROLE OF THE ANESTHETIC

While we have been able to demonstrate that death following anesthesia is the result of a generalized circulatory insufficiency in which cerebral symptoms dominate the clinical picture, it has not been established whether the anesthetic is the causative agent or merely the precipitating factor. Regardless of the anesthetic agent employed, the cerebral lesions in our 21 cases were essentially the same, although the intensity of the process varied even with the same anesthetic.

Experimentally, recent studies give a basis for the hypothesis that anesthesia alone may produce alterations in general circulatory efficiency. Harrison [8] has adequately demonstrated that a fall in blood pressure frequently occurs during spinal anesthesia.

Using ether as the anesthetic, Boyce and McFetridge [9] have shown a marked decrease in hepatic function, and Snyder,[10] using the same agent, has shown that there are a 41 per cent drop in cardiac output and a decline in blood pressure. Stewart and Rourke [4] have reported a 15 per cent loss in circulating blood volume, while Bollman, Svirbely and Mann [11] have noted hemoconcentration to occur coincidentally with ether anesthesia in experimental animals. In addition, McAllister [7] has reported an 11 per cent decrease in plasma volume.

It has been considered that such alterations in circulatory efficiency are transient. Moon [12] stated that in the experimental animal complete anesthesia per se is rarely sufficient to produce failure of the circulation. However, he cited war experience to show that anesthesia may precipitate circulatory failure (shock) under conditions in which circulation is already impaired.

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8. Harrison, T. R.: Failure of the Circulation, Baltimore, Williams & Wilkins Company, 1935.

9. Boyce, F. F., and McFetridge, E. M.: Studies of Hepatic Function by the Quick Hippuric Acid Test, Arch. Surg. **37**:401 (Sept.) 1938.

10. Snyder, J. C.: The Cardiac Output and Oxygen Consumption of Nine Surgical Patients Before and After Operation, J. Clin. Investigation **17**:571 (Sept.) 1938.

11. Bollman, J. L.; Svirbely, J. L., and Mann, F. C.: Blood Concentration Influenced by Ether and Amytal Anesthesia, Surgery **4**:881 (Dec.) 1938.

12. Moon, V. H.: Shock: Its Mechanism and Pathology, Arch. Path. **24**:642 (Nov.); 794 (Dec.) 1937.

This is in line with Ravdin and Johnston's [13] suggestion that the cumulative effects of oxygen deficit from impaired blood flow prior to anesthesia may be a factor in the production of a breakdown of normal function after surgical operation. The brain was first investigated to rule out the possibility of a circulatory factor operating locally. In this examination we studied only patients who were too young for the degenerative changes of middle life and who died within twenty-four hours after operation. In these cases, of which there were 9, we were able to demonstrate that there had been chronic circulatory insufficiency in the brain prior to induction of the surgical procedure. This was concluded on the basis of increased connective tissue around the blood vessels and in the subarachnoid space, on the presence of severe degenerative changes in the myelin sheath and particularly on the basis of perivascular demyelination. We were unable to show any local factor, such as occlusive atheromatous changes in the blood vessels, which might be responsible for local circulatory insufficiency.

From the clinical studies there is no suggestion that cardiovascular decompensation was present in any case. Nevertheless, studies of the viscera in the subgroup of young patients showed evidence of a similar process of circulatory insufficiency in all the viscera. These changes were in the nature of a parenchymatous change in the cells and an increase in connective tissue. In our entire series, although there had been no evidence of decompensation, we were able to show structural changes in the cardiovascular system which pointed to the fact that the patients had a reduced margin of circulatory efficiency.

ROLE OF LATENT CARDIOCIRCULATORY INSUFFICIENCY

This suggests that there are many cases in which there exists a latent cardiocirculatory insufficiency which under ordinary circumstances gives no clinical evidence of its presence. We are not concerned here with the possible and unavoidable "anesthetic death" which follows acute circulatory disturbances of the shock picture incident to severe trauma, abdominal catastrophes or peritonitis. We are concerned with the type of case in which there is a latent circulatory insufficiency which with the added stress of anesthesia and an acute condition requiring surgical intervention precipitates cerebral changes. Such changes are the more tragic because they are unexpected. Prior to operation the patient mentions no history or symptoms of cardiovascular disease, and when collapse is precipitated by the anesthetic, its circulatory origin is masked by the dominance of the cerebral symptoms. Such accidents can probably occur in the presence of a normal cardiocirculatory system, but in every case in our series we were able to establish a masked or

13. Ravdin, I. S., and Johnston, C. G.: Nitrous Oxide Oxygen Anesthesia and Anoxia, Am. J. M. Sc. **194**:279 (Aug.) 1937.

latent chronic circulatory insufficiency as the basis for death. The underlying causes of reduced circulatory efficiency were varied. In 6 patients cardiac hypertrophy was present (average age, 41 years), and in 6 chronic myocardial degeneration was observed (average age, 30 years). Other factors were severe secondary anemia, rheumatic valvulitis (3 cases) and old cardiac infarct (2 cases).

SUMMARY

Twenty-one cases of postoperative cerebral complications have been studied, special attention being given to the condition for which the operation was performed, the operative risk, the age of the patient and the type of anesthetic used. The postoperative cerebral symptoms are enumerated. The etiology and pathology of cerebral complications are discussed, as are the parts played by the anesthetic and by the cardiocirculatory system.

The limitations of space render impossible at this time the discussion of the predisposing causes of postoperative cerebral accidents, their prevention and their treatment. These will be considered in future articles, as will the results of experimental animal investigations.

A brief abstract of each case is appended.

CONCLUSIONS

1. Cerebral complications following surgical operation are not rare.

2. Such complications are seldom the result of embolism or hemorrhage.

3. The cerebral lesion is usually diffuse, involving the entire brain.

4. Examination of the brain and other viscera reveals that cardiocirculatory efficiency usually has been impaired long before the operation is performed. This impairment is manifested chiefly by parenchymatous edema and congestion and by perivascular fibrosis. The presence of diminished circulatory efficiency is usually unsuspected.

5. Any anesthetic agent may contribute to the production of postoperative cerebral complications.

6. Cerebral complications (psychoses, coma, convulsions, paralysis) after surgical operation are frequently the sequels of relative cerebral anoxia produced by an alteration in blood pressure occurring as a result of the effect of surgical operation and of the anesthetic on a patient with impaired cardiocirculatory efficiency.

REVIEW OF CASES

Brief abstracts of the histories of the cases comprising this series are presented. In every case the brain showed widespread degenerative changes dependent on the effects of acute anoxia. There was also

evidence of a chronic circulatory insufficiency as manifested by perivascular demyelination and perivascular fibrosis. Factors we consider as predisposing to latent cardiocirculatory insufficiency are enumerated under the postmortem observations in each case.

CASE 1.—J. G., aged 9, was admitted to the service of Dr. E. L. Eliason. On admission there was extreme tenderness in the right lower quadrant of the abdomen. Operation was done March 2, 1936, with nitrogen monoxide, oxygen and ether anesthesia. There was no evidence of peritonitis, but the appendix was bound down under the liver as a result of nonrotation of the cecum. Appendicostomy was performed. On March 3 the patient was restless and irrational. Death occurred the same day, the temperature being 108 F. fifteen hours after operation.

Postmortem Study.—Cultures of blood from the heart and material from the peritoneal cavity were sterile. The kidneys showed bilateral hydronephrosis. The liver showed fatty infiltration. There was hypoplasia of the circle of Willis.

CASE 2.—Miss R. H., a Negress aged 20, was admitted to the hospital from the service of Dr. John McGlinn. She was a primipara and had been followed in the "prenatal clinic" for five months before her admission Feb. 19, 1936, in labor. The blood pressure was 115 systolic and 70 diastolic. Low application of a Simpson forceps was done with the patient under nitrogen monoxide and oxygen anesthesia. There was moderate bleeding. The placenta was manually removed. The uterus was packed. The patient went into circulatory collapse shortly thereafter and did not recover.

Postmortem Study.—The postmortem diagnosis was sickle cell anemia.

CASE 3.—Miss A. G., white, aged 25, was transferred to the service of Dr. E. L. Eliason. She was admitted to the hospital Feb. 11, 1938, because of jaundice. The blood pressure was 118 systolic and 40 diastolic. The erythrocyte count was 1,200,000 and the leukocyte count, 4,200 per cubic millimeter of blood. The volume index was 1.1. The Kahn reaction was 4 plus. The medical diagnosis was hemolytic anemia. On March 26 splenectomy was performed because of splenomegaly. Cyclopropane anesthesia was employed. Left hemiplegia was noted on March 30, and the patient died April 4 with a temperature of 104 F.

Postmortem Study.—The brain showed an anomalous circle of Willis. There was severe hemolytic anemia.

CASE 4.—Mrs. M. K., a Negress aged 27, in the service of Dr. Frank Hammond was admitted to the hospital Oct. 22, 1934. The past history was irrelevant. Physical examination revealed no abnormality. The blood pressure was 100 systolic and 65 diastolic. The Kahn reaction was negative. On October 24 a perineorrhaphy and a bilateral salpingectomy were performed with the patient under nitrogen monoxide, oxygen and ether anesthesia. On October 24 clinical evidence of shock (coma) was noted. On October 30 there were confusion and convulsions. After this the patient was confused and incontinent until death, which occurred on November 2 with a temperature of 103 F.

Postmortem Study.—The heart showed chronic rheumatic valvulitis. The liver showed fatty degeneration.

CASE 5.—Mr. A. D., white, aged 27, was transferred to the service of Dr. Harvey Righter. He was admitted June 22, 1934, to the psychopathic department. He was

chronically alcoholic. The symptoms and the blood picture were suggestive of hyperinsulinism. The electrocardiogram showed myocardial weakness. The blood pressure was 100 systolic and 60 diastolic. Nitrogen monoxide, oxygen and ether anesthesia was used. No definite tumor was found, but the tail of the pancreas was resected. Postoperative shock (coma) was noted. He died September 4 with a temperature of 108 F.

Postmortem Study.—The heart showed hypertrophy with severe degeneration. The liver showed fatty infiltration.

CASE 6.—Mrs. A. J., a Negress aged 28, was a patient in the service of Dr. Frank Hammond. She had attended the "prenatal clinic" and was admitted to the hospital in labor on Nov. 2, 1935. She was a primipara and was obese. Sugar was observed in the urine at various times ante partum. The Wassermann reaction of the blood was 4 plus. The blood pressure was 176 systolic and 100 diastolic. During induction of anesthesia with nitrogen monoxide and oxygen she suddenly stopped breathing and could not be revived. The child was not delivered.

Postmortem Study.—The heart showed cardiac hypertrophy. The brain showed a hypoplastic circle of Willis.

CASE 7.—Mrs. L. O., a Negress aged 28, in the service of Dr. Hubley Owen, was admitted to the hospital March 15, 1935. She had taken salts on March 12. The blood pressure was 140 systolic and 75 diastolic. Appendectomy and drainage of an appendical abscess were done on March 15 with the patient under nitrogen monoxide, oxygen and ether anesthesia. There were convulsions for four days before death. The patient died March 20, with a temperature of 108 F.

Postmortem Study.—There was a well walled-off pelvic abscess. The heart showed severe myocardial degeneration with atheroma of the aorta. The liver showed hemosiderosis. The lungs showed atelectasis.

CASE 8.—Mrs. E. C., a Negress aged 31, in the service of Dr. Frank Hammond, was admitted to the hospital on Nov. 13, 1934. There was a history of occasional dyspnea on exertion and dizziness. The blood pressure was 120 systolic and 80 diastolic. Cardiac examination gave negative results. Slight pitting edema of the ankles was present. The Kahn reaction was negative. Operation (hysterectomy and appendectomy) was performed November 15 with nitrogen monoxide, oxygen and ether anesthesia. The immediate reaction was good, but several hours later shock (coma) was noted. The patient died November 16.

Postmortem Study.—There was a moderate secondary hemorrhage (1 liter) in the pelvis. The heart was hypoplastic and showed severe myocardial degeneration.

CASE 9.—Dr. W. V., a white man aged 32, in the service of Dr. J. O. Bower, Dr. P. McCarthy and Dr. J. R. Moore, was admitted to the hospital April 20, 1933, with fracture of both femurs following an automobile accident. After open reduction both femurs were involved by chronic osteomyelitis. Thirteen operations were subsequently performed. After the last operation, performed Sept. 13, 1936, with spinal anesthesia, the patient showed evidence of shock. Right hemiplegia was noted. The patient died October 3.

Postmortem Study.—There was atrophy of the iliac arteries and veins, with a recanalized thrombus of the inferior vena cava. The aorta showed a partially organized mural thrombus. The brain showed an anomalous circle of Willis.

CASE 10.—Mr. W. C., a Negro aged 33, in the service of Dr. Louis Englerth, was admitted to the hospital July 1, 1935. He had been a typhoid carrier since 1933. The blood pressure was 105 systolic and 70 diastolic. Cardiac examination gave negative results. The urine gave a 2 plus reaction for albumin. The Kahn reaction was negative. Cholecystectomy was performed July 3. Procaine hydrochloride (spinal) anesthesia was used. The blood pressure was 180 systolic and 120 diastolic. After administration of the anesthetic and during the operation the blood pressure fell rapidly and the respirations became shallow, ceasing twenty minutes after the anesthetic was given. Artificial respiration and intravenous dextrose were used, but to no avail.

Postmortem Study.—The heart showed concentric hypertrophy of the left ventricle.

CASE 11.—Mr. L. L., white, aged 33, in the service of Dr. Louis Englerth, was admitted to the hospital Oct. 12, 1935. There was a history of pain in the right side since December 1. The patient was markedly obese. The urine gave a 3 plus reaction for albumin and contained sugar. The blood pressure was 145 systolic and 95 diastolic. Operation (appendectomy for a gangrenous ruptured appendix) was performed December 10, with nitrogen monoxide, oxygen and ether anesthesia. On December 11 the patient was stuporous. Weakness was noted on the right side. He died December 12, with a temperature of 105 F.

Postmortem Study.—The heart showed hypertrophy. The liver showed fatty degeneration. The brain showed a hypoplastic circle of Willis.

CASE 12.—Mrs. J. W., a Negress aged 33, in the service of Dr. Harvey Righter, was admitted to the hospital March 6, 1929, for an incomplete abortion. There had been profuse bleeding from March 3 until admission. Edema of the ankles and palpitation had been noted during pregnancy. The heart was enlarged, the rhythm was irregular. The blood pressure was 160 systolic and 90 diastolic. The Kahn reaction was 4 plus. Dilation and evacuation of the uterus were done with the patient under nitrogen monoxide anesthesia. She stopped breathing at the end of the operation, and artificial respiration was instituted. She recovered temporarily, but right hemiplegia and flaccidity of the extremities developed on March 20. She died March 23. The temperature at death was 107 F.

Postmortem Study.—The liver showed fatty degeneration.

CASE 13.—Mrs. A. K., white, aged 36, in the service of Dr. P. McCarthy, was admitted to the hospital Sept. 17, 1935. The systolic blood pressure varied between 160 and 204, the diastolic pressure being 110. The clinical picture of the Cushing syndrome had been present for two years. Exploratory laparotomy was done November 1 for a possible tumor of the adrenal gland, cyclopropane anesthesia being employed. No tumor was found, but the left adrenal gland and the tail of the pancreas were removed. The patient responded poorly to the operation and died, apparently from shock, November 3.

Postmortem Study.—The heart showed severe myocardial degeneration with fragmentation. The liver showed fatty degeneration. The kidneys showed nephrosclerosis.

CASE 14.—Mrs. E. D., white, aged 42, in the service of Dr. C. A. Behney, was admitted to the hospital Feb. 18, 1936, because of uterine bleeding. The urine gave a 3 plus reaction for sugar and a 2 plus reaction for albumin. A hysterectomy, a bilateral salpingo-oophorectomy and an appendectomy were performed because of a fibroid tumor. The blood pressure was 208 systolic and 98 diastolic. The

erythrocyte count was 3,000,000 per cubic millimeter of blood. The Wassermann reaction of the blood was 4 plus. Ether anesthesia was used. The patient lived eighteen hours after the operation. She was irrational, and tonic spasms were noted. She died February 20 with a temperature of 104 F.

Postmortem Study.—The heart showed a healed cardiac infarct.

CASE 15.—Mrs. S. B. V., white, aged 43, in the service of Dr. Harvey Righter, was admitted to the hospital Aug. 12, 1926. There was a history of chronic glomerular nephritis, allergy to food and drugs and dyspnea on exertion for one year. Appendectomy was performed August 12, with nitrogen monoxide and oxygen anesthesia. The patient collapsed after the operation, while still in the operating room, and never recovered consciousness. She died August 14.

Postmortem Study.—The heart showed hypoplasia.

CASE 16.—Mrs. M. S., white, aged 49, in the service of Dr. E. L. Eliason, was admitted to the hospital March 22, 1936, because of weakness, dyspnea on exertion and pain in the right leg. Physical examination showed cardiac enlargement, mitral stenosis, auricular fibrillation and evidence of occlusion of the right femoral artery. The blood pressure was 170 systolic and 80 diastolic. The value for blood sugar was 163 mg. per hundred cubic centimeters. On April 1 a midthigh amputation was performed on the right, with nitrogen monoxide, oxygen and ether anesthesia. On April 2 the patient was mentally confused. She died April 3, with a temperature of 102 F.

Postmortem Study.—The heart showed chronic rheumatic valvulitis.

CASE 17.—Mrs. S. S., white, aged 53, was admitted to the hospital from the service of Dr. Harvey Righter. The past history was irrelevant. Cardiac examination gave negative results. The blood pressure was 134 systolic and 82 diastolic. On Aug. 11, 1934, incision and drainage were done for tenosynovitis of the fourth finger of the left hand. Nitrogen monoxide and oxygen anesthesia was used. Reoperation was performed September 4, with incision and drainage for tenosynovitis of the left hand. The same anesthetic was used. The patient stopped breathing during the operation and remained in coma for five hours. Thereafter she was irrational until death, which occurred September 7 with a temperature of 105 F.

Postmortem Study.—The heart showed severe myocardial degeneration. The liver showed portal cirrhosis and fatty degeneration.

CASE 18.—Mr. S. P., white, aged 57, was transferred to the service of Dr. E. L. Eliason. He was known to have had diabetes for four years. He was admitted to the hospital in stupor on Aug. 10, 1935. The value for blood sugar was 200 mg. per hundred cubic centimeters. The erythrocyte count was 2,920,000 per cubic millimeter, with 50 per cent hemoglobin. The leukocyte count was 8,100 per cubic millimeter. The carbon dioxide-combining power was 50 volumes per cent. The blood pressure was 130 systolic and 80 diastolic. On August 10 a midthigh amputation was done for an infected, gangrenous foot. The stump was left open. Cyclopropane anesthesia was used. Clonic movements were noted shortly after the operation. The patient died August 15 with a temperature of 106 F.

Postmortem Study.—The heart showed calcified aortic and mitral valves with mitral stenosis. There was concentric hypertrophy. The liver showed early portal cirrhosis.

CASE 19.—Mrs. A. S., white, aged 62, was transferred to the service of Dr. Louis Englerth. She was admitted in coma to the metabolic department on Aug. 16, 1937. There was transient weakness of the right side of the body nine days before admission. The blood pressure was 135 systolic and 35 diastolic. Infection of the right foot was noted. The coma responded to medical treatment. Amputation of the right leg at the midthigh was done on August 17, with cyclopropane anesthesia. Complete right hemiplegia was noted on August 19. The patient died on that day, with a temperature of 108 F.

Postmortem Study.—The heart showed severe atheroma of the coronary arteries and aorta and hypertrophy. The kidneys showed acute pyelonephritis. The brain showed an anomalous circle of Willis.

CASE 20.—Mrs. E. S., white, aged 65, was transferred to the service of Dr. Louis Englerth. She was admitted to the hospital Aug. 11, 1934. She was known to have had diabetes for eight years. The blood pressure on admission was 142 systolic and 62 diastolic. The value for hemoglobin was 60 per cent. The liver was palpable 6 cm. below the costal border. The preoperative blood pressure was 90 systolic and 52 diastolic. Laparotomy was performed because of partial intestinal obstruction. Empyema of the gallbladder was found. Partial cholecystectomy was performed with nitrogen monoxide, oxygen and ether anesthesia. Postoperative twitching of the extremities was noted. Death occurred twelve hours after the operation.

Postmortem Study.—The heart showed concentric hypertrophy with marked fibrosis of the myocardium. The brain showed the circle of Willis to be extremely hypoplastic.

CASE 21.—Mrs. R. K., white, aged 70, in the service of Dr. W. W. Babcock, was admitted to the hospital Nov. 10, 1937. She was known to have had diabetes for five years. There was painful gangrene of the right leg. The blood pressure ranged between 166 and 182 systolic and 70 and 90 diastolic. There was a systolic aortic and mitral murmur. A midthigh amputation was performed Jan. 1, 1938, with cyclopropane anesthesia. The patient showed confusion and catatonia. She died January 17 with a temperature of 102 F.

Postmortem Study.—The heart showed a healed cardiac infarct. The liver revealed parenchymatous and fatty degeneration. The kidneys showed benign and malignant nephrosclerosis. The brain showed anomalies of the circle of Willis.

ABSTRACT OF DISCUSSION

DR. HENRY K. BEECHER, Boston: The questions raised by Dr. Behrend and Dr. Riggs are so controversial that it is not likely that they will be completely settled for a long time. Dr. Behrend assigns a role of primary importance to preexisting latent circulatory impairment in the causation of neurologic complications. With that concept I must disagree. It is possible that that explanation accounts for the complications observed in some cases, although accumulation of convincing evidence on that score is difficult.

Patients who do not die at once of severe anoxia are bound to show considerable evidence of damage. For a certain period, at least, this evidence increases. The difficulties of distinguishing preexisting from postaccidental injuries increase with the length of time the patient survives after the accident.

Many more cases than have been reported by Drs. Behrend and Riggs would be necessary to establish reasonable certainty of the significant presence of preexisting vascular lesions.

Most persons pass through a considerable period of anoxia before death occurs. Would it not be advisable, even necessary, to control the observations reported by an examination of pathologic material from patients who do not belong in this series, that is, by an examination of ordinary autopsy material to check the general frequency of evidences of old, latent circulatory impairment?

I should like to ask Dr. Behrend and Dr. Riggs why it is (if preexisting latent circulatory impairment is of such importance) that these neurologic complications do not occur with some regularity in patients with frank circulatory lesions. It is my observation that they do not customarily occur in patients with frank cardiac or circulatory defects.

Convulsions occurring during anesthesia are one of the most dramatic forms of complication. The single point on which everybody seems to be agreed concerning such convulsions is that they characteristically occur in children and in young adults. Surely it would not be contended that latent circulatory impairment is more common in this group.

In five years general anesthesia has been used in some 45,000 cases at the Massachusetts General Hospital. There have been nine convulsions in 8 patients. Roughly, one-half (25,000) of the patients were charity patients; 20,000 were private patients; 15,000 of these private patients were anesthetized by essentially the same staff and by the same technics as the charity patients; yet all of the convulsions occurred in the charity patients. There is no evidence, so far as I know, that such patients are more apt to have latent circulatory impairment than others.

I do not believe that one has any right to assign a greater importance to one suggested mechanism than to another. I agree with Dr. Behrend and Dr. Riggs that anoxia is a probable cause of these complications. The chief evidence for this is simple but indirect; it is known that anoxia does, on occasion, produce similar lesions. Little else is certain.

Dr. F. H. Lewy, Philadelphia: I should like to mention one aspect of the mechanism of the phenomenon. It is a well known fact that "high-strung" persons are not good risks for narcosis. The good result of preoperative application of sedatives in preventing the operative shock suggests that the vasomotor nervous system may play a part in the conditions here described.

Anoxia of the brain cells, on the other hand, may be the direct consequence of angiospasms of the cerebral blood vessels or may follow peripheral vasomotor paralysis. I should like to ask whether the history or the results of examination of any of the patients of Dr. Behrend and Dr. Riggs suggested the presence of constitutional vasolability and whether the condition of the patients spoke more in favor of angiospasm or paralysis.

Dr. Albert Behrend, Philadelphia: It is essential for the surgeon to understand the importance of maintaining a supply of oxygen particularly to the brain but also specifically to the liver, kidneys and heart of a patient during and after an operative procedure. More and more surgery is becoming applied physiology. Ability to prevent many little understood postoperative complications involving the liver, kidneys, cardiovascular system and brain will depend on a better understanding of the physiology of these organs.

The patients in this series were all operated on in a city institution. In the cases of most of them cardiac and circulatory disorders were neither apparent nor suspected. I think that cerebral accidents occur in the presence of known cardiac and circulatory disease, but their relative infrequency may be attributed to the

fact that in such cases great care is taken to avoid complications during the period of operation. However, experienced clinicians all emphasize the difficulty of forecasting the response of a patient with cardiac disease to operation.

Dr. Lewy has brought up a point of some importance. We have had a patient who showed evidence of a very labile neurocirculatory mechanism. The patient was a typhoid carrier admitted to the hospital for cholecystectomy. In the course of routine examination he showed a blood pressure of 110 mm. of mercury systolic. Under the stress of preoperative anxiety his blood pressure rose to 160 mm. of mercury systolic. He was then given a spinal anesthetic, and his blood pressure rapidly dropped, so that in forty minutes there was gradual slowing of the respiration and circulation and the patient died despite all efforts to restore him. Greater knowledge of the nervous control of the circulatory system may help to explain postoperative shock in some cases.

TISSUE METABOLISM AND PHOSPHATASE ACTIVITY IN EARLY CALLUS

J. P. TOLLMAN, M.D.
OMAHA

D. H. DRUMMOND, M.D.
DAYTON, OHIO
AND
A. R. McINTYRE, M.D.
AND
J. DEWEY BISGARD, M.D.
OMAHA

In 1930, Kay [1] observed a rise in the level of serum phosphatase following fracture and suggested that this might be on the basis of increased local production of phosphatase. McKeown and Ostergren [2] studied the phosphatase activity in healing fractures in albino rats. They found a rise in osseous phosphatase during callus formation and a fall during development of the medullary space. Peden [3] followed the concentration of plasma phosphatase in healing fractures in children and found a rise during the first few days, followed by a fall. Gutman, Sproul and Gutman [4] found increased phosphatase activity at the site of osteoplastic metastases secondary to carcinoma of the prostate. Botterell and King [5] studied changes in callus and blood phosphatase in rabbits. They found an increase at the site of fracture which lasted fifty to sixty days. This was seen to be related to the degree of osteoblastic activity of the callus. They found no significant changes in the phosphatase content of the blood. Wilkins and Regen [6] demonstrated

From the University of Nebraska College of Medicine.

1. Kay, H. D.: Plasma Phosphatase: II. The Enzyme in Disease, Particularly in Bone Disease, J. Biol. Chem. **89**:249, 1930.

2. McKeown, R. M., and Ostergren, J. I.: Phosphatase Content of Fractured Bone, Proc. Soc. Exper. Biol. & Med. **29**:54-56, 1931.

3. Peden, O. D.: Plasma Phosphatase and Phosphorus During Healing of Fractures in Children, Arch. Dis. Childhood **12**:87-90, 1937.

4. Gutman, E. B.; Sproul, E. E., and Gutman, A. B.: Significance of Increased Phosphatase Activity of Bone at the Site of Osteoplastic Metastases Secondary to Carcinoma of the Prostate, Am. J. Cancer **28**:485-494, 1936.

5. Botterell, E. H., and King, E. J.: Phosphatase in Fractures, Lancet **1**: 1267-1270, 1935.

6. Wilkins, W. E., and Regen, E. M.: Course of Phosphatase Activity in Healing of Fractured Bones, Proc. Soc. Exper. Biol. & Med. **32**:1373, 1935.

increased phosphatase activity at the site of fractures in rabbits, associated with a slight increase in blood phosphatase. Hunsberger and Ferguson [7] found a variable rise in values for blood phosphatase during repair of fractures. Roe and Whitmore [8] have reported a number of cases in which increased phosphatase activity was associated with proliferation of bone. Woodard, Twombly and Bradley [9] found increases in blood phosphatase in cases of bone tumor. They showed that the highest values were obtained in cases of osteogenic sarcoma. It is seen that local osseous proliferation is associated with increased local phosphatase activity and sometimes with increased values for blood phosphatase. It was felt that it would be of interest to study the relation between the phosphatase activity of the callus and its metabolic activity. Because of the necessity of using macerated tissue for the metabolic determinations, only early calluses could be used.

METHOD

Adult rabbits were used. With sterile technic the radius on one side was exposed and the periosteum separated and elevated. A portion of bone about 1 cm. in length was removed. The incision was then closed with a silk suture. Immediately before operation blood was removed from the heart for determination of the phosphatase content. Since this work is concerned with tissues having a high phosphate content, a method of determination independent of phosphate blanks was chosen. The method of King and Armstrong [10] is well adapted to this end. It was used for both tissue and blood. At progressive intervals of three to four days after operation 2 rabbits were roentgenographed and killed, and the callus was removed for study. Immediately after death blood was taken for determination of the phosphatase content. A small portion of the callus was reserved for microscopic study, and the remainder was weighed and macerated in Dixon-Ringer solution.[10a] On this extract the oxygen consumption was measured by the method

7. Hunsberger, A., and Ferguson, L. K.: Variations in Phosphatase and Inorganic Phosphorus in Serum During Fracture Repair, Arch. Surg. **24**:1052-1060 (June) 1932.

8. Roe, J. H., and Whitmore, R.: Clinicopathologic Application of Serum Phosphatase Determination with Special Reference to Lesions of the Bones, Am. J. Clin. Path. **8**:233-254, 1938.

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10. King, E. J., and Armstrong, A. R.: A Convenient Method for Determining Serum and Bile Phosphatase Activity, Canad. M. A. J. **31**:376, 1934.

10a. Dixon-Ringer solution is composed of the following ingredients: 100 cc. of solution of sodium chloride (0.9 Gm. per hundred cubic centimeters), 2 cc. of solution of potassium chloride (1.19 Gm. per hundred cubic centimeters), 2 cc. of solution of calcium chloride (1.47 Gm. per hundred cubic centimeters), 2 cc. of 10 per cent dextrose.

The mixture was boiled for fifteen minutes, cooled in oxygen free from carbon dioxide, and made up to the original volume with water free from carbon dioxide.

of Warburg.[11] The phosphatase was then extracted, the mixture being allowed to stand in the ice box for thirty-six hours and the supernatant fluid was used for determination of the value for tissue phosphatase. Because of the small amount of tissue available, separate specimens could not be taken to determine the calcium content. As the calcium studied was insoluble, however, it was felt to be sufficiently accurate to use the tissue residue from the extraction for this purpose. Organic matter was removed by digestion with concentrated nitric acid, and the calcium content was determined by a modification of the method of Clark and Collip.[12]

RESULTS

The results of this work are presented in table 1. The data are on a basis of the wet weight of the tissue with the exception of the oxygen consumption, which is expressed in a conventional manner, Q_{O_2} being

TABLE 1.—*Tissue Metabolism and Phosphatase Activity in Early Callus*

Age of Fracture, Days	Sex of Animal	Blood Phosphatase		Weight of Callus, Mg.	Phosphatase, Units/Gm.	Q_{O_2}*	Calcium, Mg./Gm. of Tissue
		Initial Value	Final Value				
4	F	3.1	2.4	144	153	—3.72	...
4	F	4.3	9.2	165	154	—3.47	...
7	F	6.2	2.0	65	216	—4.15	4.6
7	F	2.8	3.8	285	21	Failure	0.7
9	F	2.3	3.2	152	580	—6.80	3.3
9	F	5.6	3.9	182	1,050	—3.78	13.2
10	M	4.3	9.6	101	276	—1.75	5.9
10	F	1.8	6.1	65	154	—2.75	3.1
12	F	26.6	18.7	82	850	—2.55	9.8
12	F	23.8	12.6	105	3,480	—0.10	20.0
12	F	2.8	6.0	105	200	—0.20	8.6
12	F	6.1	4.0	144	550	—5.20	3.5

* Oxygen consumption in cubic millimeters per milligram of dry weight of tissue in one hour.

the consumption of oxygen in cubic millimeters per milligram of dry weight of tissue per hour. In tables 2 and 3 the changes in roentgen and microscopic appearance are outlined.

There appeared to be a considerable variation in the values representing the metabolic rate, which was due to the inherent error of this type of determination plus individual variations in the callus. There was on the average a falling off in metabolic activity as the age of the callus increased. This must have been due to decreased activity of the tissues rather than to replacement by calcium, since the amount of calcification present in the early callus was not sufficient to affect materially the

11. Warburg, O.: Ueber die Rolle des Eisens in der Atmung des Seeigeleis nebst Bemerkungen über einige durch Eisen beschleunigten Oxydationen, Ztschr. f. physiol. Chem. **92**:231-256, 1914.

12. Clark, E. P., and Collip, J. B.: Tisdall Method for Determination of Blood Serum Calcium with a Suggested Modification, J. Biol. Chem. **63**:461-464, 1925.

amount of active tissue present. The results obtained here are in substantial agreement with those given by Neuhaus.[13]

The degree of calcification showed a general increase with age of the callus, but this also showed some variability. This was due in part to the possibility of varying degrees of decalcification of the ends of

TABLE 2.—*Roentgen Appearance of Healing Fractures*

Age of Fracture, Days	Roentgen Appearance
4	Sharp osteotomy defect; no callus; no decalcification of fragments
4	Similar to previous specimen, small bone chip present
7	Possible early decalcification of bone adjacent to osteotomy
7	Traumatic fracture of ulna; marked soft tissue swelling
9	Slight soft tissue swelling; early increased density throughout defect
9	Similar to previous specimen
10	Definite patchy calcium deposition in defect; some decalcification of fragments
10	Similar to previous specimen
12	Marked but somewhat patchy calcium deposition in osteotomy defect
12	Similar to previous specimen, but callus thicker and not limited to region of defect
12	Rather dense patchy calcification, but quantity much less than in previous two specimens
12	Slight patchy calcification

TABLE 3.—*Microscopic Appearance of Healing Fractures**

Age of Fracture, Days	Tissue Elements
4	Fibroblasts, capillaries; small capillaries
4	Fibroblasts, fibrous tissue; relatively few vessels
7	Dense fibrous tissue; early calcification; osteoblastic differentiation
7	Fibrous tissue; early calcification; necrosis; cellular infiltration
9	Young bone spicules with fibrous tissue among them
9	Dense fibrous tissue; centers of early ossification
10	Extensive young bone formation
10	Dense fibrous tissue; early calcification
12	Dense fibrous tissue; early calcification
12	Extensive young bone formation
12	Fibrosis; slight calcification
12	Fibrosis; slight calcification

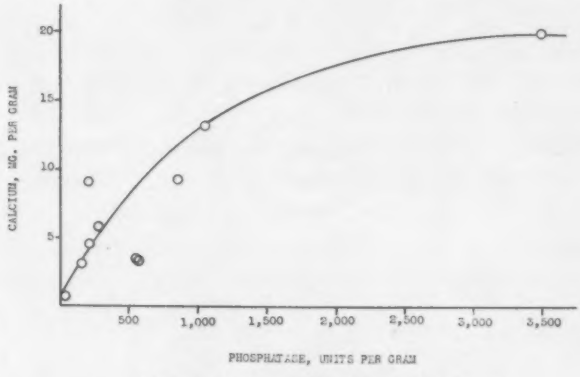
* In interpretation of the microscopic material it must be remembered that these sections may not all be representative because of the small amount of tissue available. The larger pieces were taken for metabolic studies.

the bone at either side of the osteotomy; also, small bone chips or bone dust left in the osteotomy defect may have had some effect on the amount of calcification, either by the addition of calcium compounds as such or by early assimilation of the minerals in the formation of new bone. Specimens having a high calcium content showed microscopically

13. Neuhaus, C.: Ueber den Stoffwechsel des Granulationsgewebes (Atmung und Glykolyse), Beitr. z. path. Anat. u. z. allg. Path. **83**:383-430, 1929.

the best developed bone, with formation of well defined spicules. Leriche and Jung,[14] in studying local utilization of calcium at sites of fracture, found a similar variability and generally a similar degree of calcification of the early callus. They ascribed the variations to varying degrees of decalcification of the fragments and of utilization of the mineral elements in laying down new bone. This effect was probably less in our work, since a rather large defect existed because of the osteotomy. Their results were obtained with callus from reduced human fractures.

The phosphatase activity started at a relatively low value, rising with active proliferation of bone. Because of the necessity of using soft tissue preparations this could not be followed far, but, as has been shown by other workers, the concentration may be expected to fall during restoration of the medullary cavity. In spite of the variability



Phosphatase activity in early callus.

shown in the values for the different quantities studied, there was close correlation between the amount of calcification and the phosphatase activity. Fractures showing extensive calcium deposition in the callus with good roentgen evidence of early union and microscopic evidence of new bone formation all showed high levels of phosphatase activity. In combination with the lack of correlation between the other quantities this is strong evidence that the rapidity of healing of the fracture is dependent on the amount of phosphatase produced locally. In this study, the degree of healing in the early stages was not dependent so much on the age of the fracture as on the amount of phosphatase that has been produced. This was particularly well illustrated in the case of the second rabbit killed on the seventh day. The phosphatase activity

14. Leriche, R., and Jung, A.: Documents concernant l'utilisation locale du calcium provenant d'un foyer d'ostéolyse; étude sur les mécanismes de l'ostéogenèse, Rev. de chir., Paris **76**:378-381, 1938.

was about one-tenth that observed in the first rabbit studied on the same day. The amount of calcification was also greatly less. Grossly and microscopically the region showed evidence of infection. This suggests that infected fractures show delayed healing, in part due to decreased phosphatase activity.

There was no definite shift in the values for blood phosphatase. As many values were below the initial level as were above it, and the mean showed no significant change. This is in agreement with the work of other investigators, who have found that there is no definite relation between the level of blood phosphatase and the healing of fractures.

SUMMARY

The relation of blood phosphatase, tissue phosphatase, tissue calcium and tissue metabolism was studied in a series of rabbits subjected to osteotomy.

There was an initial rise in tissue metabolism of the callus, followed by a fall. There was an irregular increase in phosphatase activity and calcium deposition with time. The changes in concentration of serum phosphatase were not characteristic.

A close relation was found between the phosphatase activity of the callus and the amount of calcium deposition.

PHOSPHATASE ACTIVITY OF INFECTED FRACTURES

D. H. DRUMMOND, M.D.
DAYTON, OHIO
AND
J. P. TOLLMAN, M.D.

J. DEWEY BISGARD, M.D.
AND
D. ROSS, M.D.
OMAHA

In the course of an earlier investigation [1] it was noted that a healing infected fracture showed a much lower level of phosphatase activity than did a sterile one of the same age. This suggested that retarded or suspended healing of infected fractures may be the result of diminished phosphatase activity. The literature concerning the relation between fractures and phosphatase activity in blood and bone has been reviewed previously.[1] It has been pointed out by Roe and Whitmore [2] in a clinical study of phosphatase activity in chronic infections of bone that there was no uniform rise in the phosphatase content of the blood.

METHOD

Bilateral osteotomy with block resection of 1 cm. of the shaft was done on the radiuses of adult rabbits, and at the same time blood was removed from the heart for initial determinations of the level of phosphatase. The osteotomy wound on one side was closed by a sterile technic. The osseous defect produced on the other side was infected by injecting into it 0.1 cc. of a broth suspension of hemolytic streptococci. With the first animal of the series it was found that, although during the first week an inflammatory change was maintained, at the end of two or three weeks the infected side showed good healing and was indistinguishable from the sterile side. This series (3 rabbits), in which there was rapid healing of the fractures, has been designated series A. In order to maintain infection for a longer time a special technic was employed. The broth suspension of the organism was placed in a small gelatin capsule, which was sealed with collodion; the capsule

From the University of Nebraska College of Medicine.

1. Tollman, J. P.; Drummond, D. H.; McIntyre, A. R., and Bisgard, J. D.: Tissue Metabolism and Phosphatase Activity in Early Callus, Arch. Surg., this issue, p. 43.

2. Roe, J. H., and Whitmore, R.: Clinicopathologic Application of Serum Phosphatase Determination with Special Reference to Lesions of the Bones, Am. J. Clin. Path. **8**:233-254, 1938.

was then placed in the space between the bone fragments at the site of the osteotomy. This had the effect of sharply localizing the infection, allowing slow diffusion of the infected material into the tissues as the capsule disintegrated and adding a foreign body to help in keeping up the inflammatory change. By this method active infection was maintained for three weeks, after which the infected side showed healing to a degree only slightly inferior to that shown by the sterile side. This series of animals, with slowly healing fractures, has been designated as series B. At progressive intervals of one week postoperatively a rabbit was killed, blood was taken for determination of the level of serum phosphatase and the callus was dissected out from either side. After a small fragment had been removed for microscopic examination, each callus was weighed, macerated with 5 cc. of 0.85 per cent solution of sodium chloride and allowed to stand in the ice box for twenty-four hours to extract the phosphatase. One cubic centimeter of the supernatant fluid was used for determination of the phosphatase content by the method of King and Armstrong.[3] Determination of the value for serum phosphatase was made at the same time. The residual saline solution together with the fragments of tissue was evaporated to dryness at 110 C. to obtain the dry weight of the specimen. The organic matter of the residue was decomposed by evaporation with nitric acid and ignition at red heat. The inorganic matter was taken up in nitric acid and was transferred to a centrifuge tube for determination of the calcium content by the method of Clark and Collip.[4]

RESULTS

The results of this work are summarized in tables 1 and 2. Both the dry and the wet weight of the tissue have been used in calculating the results. The dry weight was determined, since it has usually been considered as the primary standard of weight, but we feel that the wet weight is more significant here. Since the early callus is soft, edematous granulation tissue which is rather bulky, the wet weight more truly approximates the weight of active tissue present. Calculations based on the dry weight of such loose edematous tissue give rise to abnormally high values for phosphatase and calcium.

The first part of table 1 shows the changes in rabbits with rapidly healing infections. It is seen that the initial level of phosphatase was much lower in the infected side, and there was, similarly, a much smaller amount of calcium. For the sterile side there was a higher value for phosphatase and an increased amount of calcium. As the infected side began to heal and overcome the infection, it approached closely the characteristics of the sterile side. In fractures two and three weeks of age it was difficult to distinguish grossly or microscopically between the infected and the sterile side. This similarity in appearance was associated with almost identical values for calcium and phosphatase.

3. King, E. J., and Armstrong, A. R.: A Convenient Method for Determining Serum and Bile Phosphatase Activity, Canad. M. A. J. **31**:376, 1934.

4. Clark, E. P., and Collip, J. B.: Tisdall Method for Determination of Blood Serum Calcium with a Suggested Modification, J. Biol. Chem. **63**:461-464, 1925.

Nevertheless, the mean values for the 3 rabbits of this series showed a difference in the levels of phosphatase and calcium between the infected and the noninfected side.

TABLE 1.—*Phosphatase Activity of Infected Fractures*

Age of Fracture, Days		Weight of Callus, Mg.		Phosphatase in Callus, Units/Gm.		Calcium in Callus, Mg./Gm.		Blood Phosphatase	
		Wet	Dry	Wet	Dry	Wet	Dry	Initial	Final
	Series A								
7	Sterile	89	28	1,200	3,800	9.4	30		
	Infected	65	14	246	1,140	0.5	2.1	11.6	14.7
14	Sterile	59	31	2,000	3,800	108	204		
	Infected	58	30	2,300	4,400	78	150	5.6	9.3
21	Sterile	55	35	1,300	2,100	126	200		
	Infected	30	19	1,300	2,000	87	137	2.5	3.8
	Series B								
7	Sterile	37	8	1,500	7,100	28	130		
	Infected	45	19	220	530	5	11	7.3	9.2
14	Sterile	72	14	2,000	10,000	39	200		
	Infected	82	11	230	170	6.8	51	6.1	11.0
21	Sterile	68	37	1,800	3,400	62	300		
	Infected	106	48	400	1,000	10	23	3.5	7.6
28	Sterile	50	31	1,500	2,400	102	165		
	Infected	110	54	1,200	2,500	23	47	5.8	9.7
35	Sterile	54	35	2,300	3,500	58	90		
	Infected	52	20	500	1,400	8.1	13	4.7	6.0

	Mean Values for Calcium and Phosphatase	
	Calcium in Wet Callus, Mg./Gm.	Phosphatase in Wet Callus, Unit/Gm.
Series A		
Sterile	81	1,500
Infected	55	1,300
Series B		
Sterile	58	1,800
Infected	11	510

TABLE 2.—*Changes in Blood Phosphatase*

	Initial	Final
Series A		
7 days	11.6	14.7
14 days	5.6	9.3
21 days	2.5	3.8
Mean	6.6	9.3
Series B		
7 days	7.3	9.2
14 days	6.1	11.0
21 days	3.5	7.6
28 days	5.8	9.7
35 days	4.7	6.0
Mean	5.5	8.7

In series B the effect of sustained infection was apparent. The infected side showed a more marked difference from the sterile one, and the difference was maintained longer. It was not until the fourth and fifth week that the gross and microscopic appearance and the phosphatase

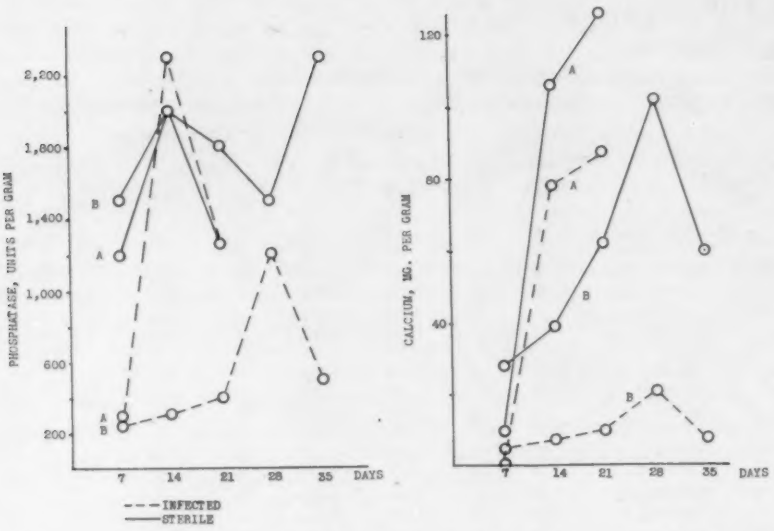


Chart 1.—Values for phosphatase and calcium in the infected and in the sterile callus.

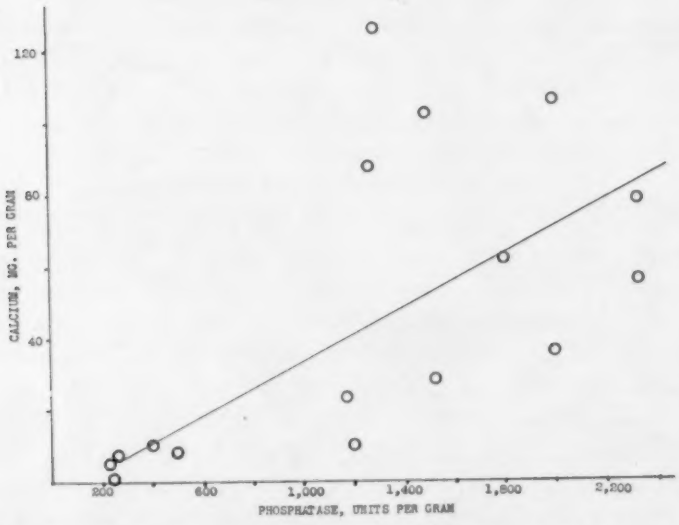


Chart 2.—Relation between the phosphatase activity and the degree of calcification.

and calcium concentration on the infected side began to resemble those on the uninfected one. This tendency for the phosphatase and calcium content of the infected callus to approach that of the sterile callus is clearly illustrated in chart 1. Chart 2 shows the relation between the phosphatase activity and the degree of calcification. This correlation is not as close as was shown previously by some of us.[1]

It will be observed that the values for blood phosphatase increased over the initial levels during the healing of the infected fractures (table 2). The consensus is that there is no characteristic change in the level of phosphatase in cases of fracture due to osteomyelitis. In our previous work[1] with sterile fractures in rabbits there was no consistent change in the values for blood phosphatase. In infected fractures there was a uniform rise above the initial values, but, since normal limits were not exceeded, determinations of the values for phosphatase in the blood would have no clinical value.

SUMMARY

In this study, the levels of phosphatase and of calcium in infected fractures in rabbits were lower than in sterile fractures.

There was a uniform rise in the level of blood phosphatase in the infected series.

In both infected and sterile fractures, high levels of phosphatase activity were associated with the presence of large calcium deposits.

THE CARPUS, WITH REFERENCE TO THE FRACTURED NAVICULAR BONE

EDWIN FRENCH CAVE, M.D.
BOSTON

When a certain fracture frequently does not respond to the forms of treatment which usually produce satisfactory results in other fractures, there is, as a rule, much speculation as to the causes of failure of healing, and many suggestions are advanced for the proper form of treatment to be employed.

Injuries to the carpal bones, with one or two exceptions, practically always heal when they are reduced properly and immobilized for a short time. The frequent exception to this rule is fracture of the carpal navicular bone. Aseptic necrosis of the lunate bone not uncommonly gives an unsatisfactory result; but dislocations and the other fractures, if promptly reduced and immobilized, are generally followed by good return of function and usefulness of the hand. Although fractures and dislocations of the carpus are not common (approximately 2 per cent of all fractures, according to a review of 4,500 fractures at the Massachusetts General Hospital), they are extremely important injuries, because failure to make a careful diagnosis of the injury, based on a thorough knowledge of the anatomy of the part, frequently results in delayed or misguided treatment, and a disabled hand may be the ultimate result.

DEVELOPMENT OF THE CARPUS

The development of the carpal bones usually follows a definite plan, and anatomic variations are infrequent. The bones are cartilaginous at birth, and during the first year the ossification centers of only the capitate and hamate bones appear. The remaining ones appear between the second and the eighth year (fig. 1), except the pisiform bone, which does not appear until the tenth year or later (fig. 2). Inflammatory processes may cause the ossification centers to appear earlier than normal (fig. 3). Tuberculosis was the exciting cause in the case illustrated. Poliomyelitis or prolonged congestion of the extremity from any cause may have the same effect. Delayed development of the carpus may occur in chondrodystrophies and as a familial characteristic, as recorded by Hess and Abramson;[1] usually these bones develop from a single ossification center, but there are exceptions. The most common of the

From the Fracture Clinic of the Massachusetts General Hospital.

1. Hess, A. F., and Abramson, H.: J. Pediat. **3**:158, 1933.

anatomic variations is the bipartite navicular bone. I have seen no such anomaly, and I wonder, as do others (Wette [2]), whether such an appearance may not always be due to an old unrecognized fracture which has produced a pseudarthrosis. Careful investigators (Dwight,[3] Todd,[4] Pfitzner,[5] Speed [6] and others), however, have reported such variations and have stated that they may also occur in the capitate bone. Usually

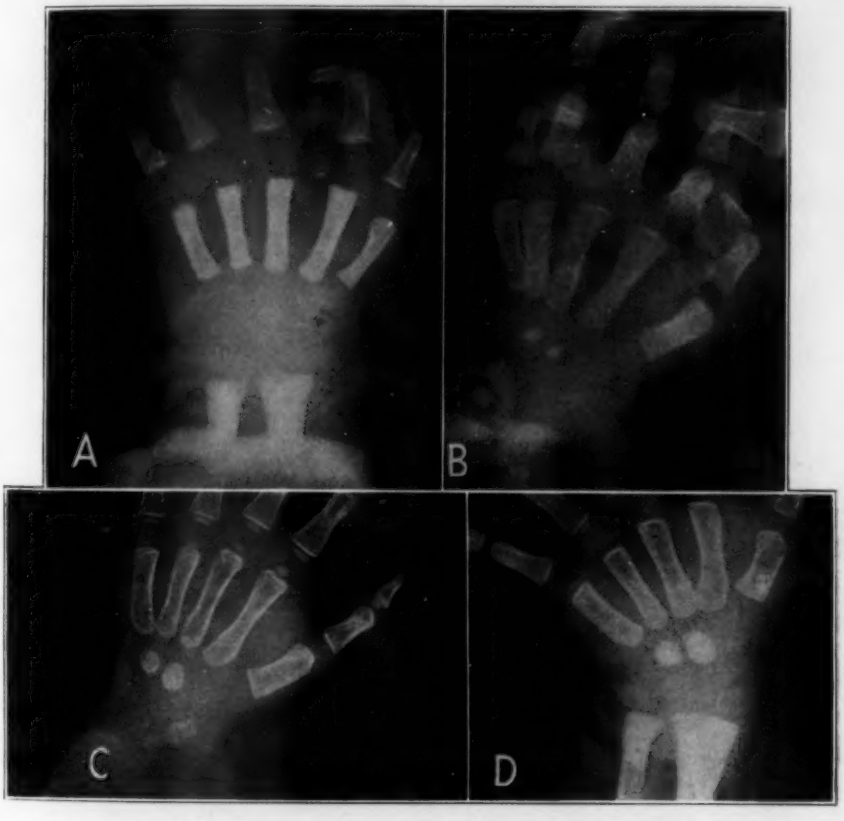


Fig. 1.—Early stages in the development of the carpus: In *A*, at birth, the carpus is entirely cartilaginous; in *B*, at 6 months, the ossification centers of the hamate and capitate bones are present; *C*, at one year; in *D*, at 2 years, the ossification centers of the hamate, capitate and triangular bones are present.

2. Wette, W.: Arch. f. orthop. u. Unfall-Chir. **29**:320, 1931.

3. Dwight, T.: Variations of the Bones of the Hands and Feet, Philadelphia, J. B. Lippincott Company, 1907.

4. Todd, A. H.: Brit. J. Surg. **9**:7, 1921.

5. Pfitzner, W.: Ztschr. f. Morphol. u. Anthropol. **2**:77, 1900.

6. Speed, K.: Traumatic Injuries to the Carpus, New York, D. Appleton and Company, 1925.

these anatomic variations are bilateral, and there may be no history of injury. Todd [4] stated that they may be associated with other congenital abnormalities, such as web fingers and premature synostosis of the phalanges. In the bipartite navicular bone, he wrote, "the line of division runs obliquely from near the outer end of the articular surface for the radius to about the middle of the concavity for the head of the os magnum" [5]—in other words, directly through the "waist" of the bone.

Fig. 2.—Later stages in the development of the carpus: In *A*, at 6 years, the capitate, hamate, triangular and lunate bones are present while the centers of the navicular and the multangular bones are just appearing; in *B*, at 7 years, all the bones are present but the pisiform bone; in *C*, at 12 years, all the bones are ossified.

Examining 1,456 wrists, Pfitzner [5] found in 9 complete bipartite navicular bones; in 29, the bone was partially cleft. Codman and Chase,[7] however, found no bipartite navicular bones in 1,040 wrists examined. No instances of failure of appearance of any carpal bone have been reported, and no accessory bones have been recorded.

7. Codman, E. A., and Chase, H. M.: Ann. Surg. **41**:321 and 863, 1905.

BLOOD SUPPLY OF THE CARPUS

The blood supply to the carpus is relatively inadequate. There are small nutrient arteries, which derive their blood supply from terminal twigs of the ulnar and radial arteries and which, after being carried

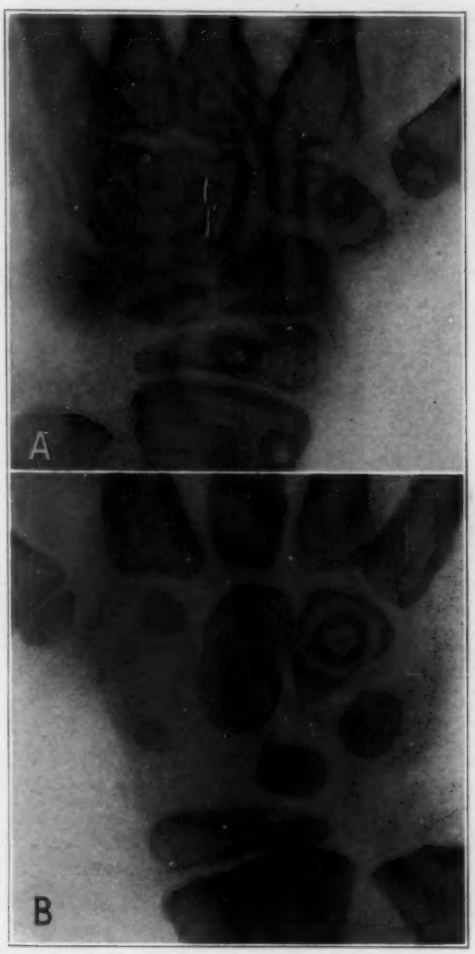


Fig. 3.—The effect of inflammation on the development of the carpus, shown by roentgenograms of both hands of a 6 year old child: In *A*, the diseased hand, all the bones are well calcified; in *B*, the normal hand, only the ossification centers of the capitate and the hamate bone are fully developed.

along supporting ligaments, enter the fibrous covering representing the periosteum. Lexer's [8] preparations showing the circulation of the navicu-

8. Lexer, cited by Küchel, W.: München. med. Wchnschr. **80**:1350, 1933.

lar bone demonstrated two nutrient vessels, one entering the tuberosity and another, a larger one, entering the middle of the body of the bone and giving off proximal and distal branches (fig. 4). Johnson [9] studied the blood supply of the navicular bone in dogs in relation to repair of bones and concluded that the supply was adequate.

ANATOMY

The importance of the anatomic arrangement of the carpal bones cannot be too strongly emphasized (fig. 5) to one who expects to treat

Fig. 4.—Blood supply to the navicular bone (after Lexer).

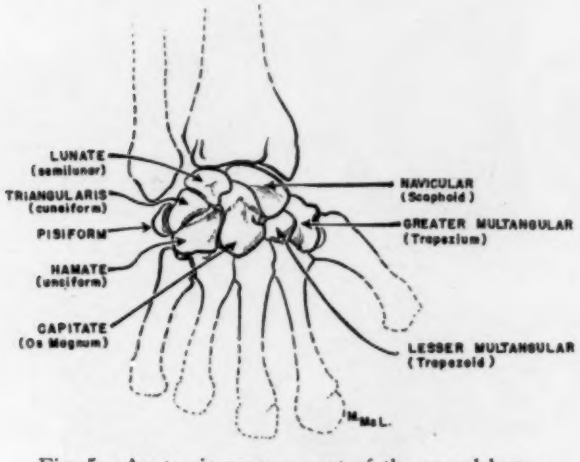


Fig. 5.—Anatomic arrangement of the carpal bones.

these carpal injuries. Indistinct fractures and minor subluxations are frequently overlooked, not through failure to take roentgenograms but through ignorance of the anatomy of the parts in various positions of the hand. Such negligence had occurred in the following case (fig. 6):

CASE 1.—J. L., a man aged 22, was admitted to the hospital on May 11, 1934. Three months before, he had fallen, striking the right wrist; he had been seen at

9. Johnson, R. W., Jr.: J. Bone & Joint Surg. **9**:482, 1927.

another hospital, where roentgenograms were pronounced normal. Two weeks before admission, the hand had been forced into dorsiflexion, increasing pain in the wrist. Roentgenograms revealed fracture of the navicular bone in the midportion. The patient was given a leather wristlet, which he wore four months. Roentgenograms at the end of that time showed bony union.

End Result.—Examination after two years showed the patient free of symptoms and his motions normal. Roentgenograms showed bony union.

Fig. 6 (case 1).—Roentgenograms of a navicular fracture: *A*, anteroposterior and oblique views made at the time of the inquiry, showing a faint line across the waist of the navicular bone, undoubtedly representing the original fracture, although the injury was not discovered in the original examination of the roentgenograms; *B*, three months later, showing a well developed fracture line; *C*, after the wearing of a leather wristlet for ten months, showing the fracture well healed.

Although the anatomy of these carpal bones is too well described in the usual textbooks to necessitate discussion here, certain facts may be emphasized. The first row of the carpus, consisting of the navicular,

lunate, triangular and pisiform bones, is on its surfaces largely cartilaginous; the remaining portions serve for ligamentous attachments. The second row, made up of the greater and lesser multangular, the capitate and the hamate bone, is less cartilaginous but is more extensively covered by the ligamentous attachments. This row is more firmly held together by the supporting ligaments than are the navicular and the lunate bone, which are more exposed to trauma because of their location and their movable articulations with the radius. On the volar surface there are tendinous attachments only to the pisiform, hamate and greater multangular bones, while on the dorsal surface there are none. The navicular bone, which is of most concern in this discussion, articulates from the dorsum with the radius, the greater and the lesser multangular bone and the lunate bone. On its volar surface the navicular bone is in contact with the greater and the lesser multangular bone, the capitate bone, the lunate bone and the radius.

PATHOLOGY

When any bone is fractured, the blood supply to the fragments is temporarily interrupted. This is particularly true of the carpal bones, and especially so of the carpal navicular bone. If the fracture line runs directly through the bifurcation of the main artery, which enters the midportion of the navicular bone, nutrition to the proximal fragment is interrupted; the distal fragment is nourished, however, by the artery entering the tubercle (fig. 4). Such interference with the blood supply to the proximal fragment explains the failure of union in a large percentage of navicular fractures in the middle and proximal regions. After immediate reduction and fixation are carried out, there is rather quick restoration of blood vessels across the fracture line. If treatment is delayed, a scar forms and the blood channels are sealed off. Even after several weeks has elapsed, it is possible to promote restoration of blood supply to the fragments if immobilization is carried out for a sufficient length of time, as illustrated in case 1. If nonunion does become established, if one or both fragments show in a roentgenogram a density greater than that of the other carpal bones, it is probable that pseudarthrosis is permanent and that no amount of fixation will promote formation of new blood vessels (fig. 7). In prolonged nonunion, vacuolation may result and only a shell of the navicular bone remain (case 13, fig. 17), the fragments taking on much the same appearance as those of the lunate bone in Kienböck's disease.

Johnson [9] in his experiments on dogs found that the fragments of the fractured navicular bone were not to any extent deprived of their blood supply. He expressed the opinion that the reparative process is carried out by cancellous bone but is slower in the navicular bone than

in the long bones and that the absence of periosteal callus is an important factor in the slow union of the navicular bone. He discounted the importance of the lytic action of the synovial fluid, a function which was advocated by Murray [10] as a factor in producing nonunion. Johnson [9] stated also that undue mobility at the fracture site is not a factor in producing delayed union, since the fragments are so closely apposed. Delayed union, therefore, is probably produced by no one factor but is brought about by a combination of excess motion, interference with blood supply, possibly the presence of synovial fluid and the absence of periosteal callus.

Fig. 7.—Nonunion of the fractured navicular bone, complete and permanent. Possibly a bone graft and drilling may produce union, but external fixation never will.

DIAGNOSIS BY ROENTGEN EXAMINATION

The hand may be placed in various positions so that in the roentgenogram the bones may appear to have an abnormal relationship (fig. 8). If the anteroposterior view of the navicular bone is made with the wrist in radial deviation the bone may appear shortened or subluxated, whereas with the wrist in ulnar deviation the true long axis of the bone is visible and any abnormality is more easily seen. It is therefore not only important to have standardized methods of roentgen technic but also necessary to have adequate knowledge of the relationships of the carpus in the various positions of the hands. For studying

10. Murray, C. R.: Ann. Surg. **93**:961, 1931.

the navicular bone, both hands should be photographed on the same plate (fig. 9); the anteroposterior view with the hands in ulnar deviation and the oblique views with the hands in midpronation are most important.

MECHANISM, DIAGNOSIS AND TYPES OF INJURY

Fracture of the navicular bone is by far the most common injury to the carpal bones. In our series of 110 carpal injuries it occurred sixty-eight times, either alone or in conjunction with other injuries to the wrist. (The accompanying table shows the types of injuries to the carpal bones.) Patients are usually of the male sex, especially young adults who are exposed to severe trauma. In most instances the injury occurs in acute dorsiflexion of the wrist, force being applied indirectly

Fig. 8.—Apparent, not actual, fracture of the navicular bone. Roentgenograms of the hand: *A*, in radial deviation, showing an apparent fracture of the navicular bone; *B*, in ulnar deviation, showing long axis of the bone and revealing no fracture.

Types of Injuries of the Carpal Bones

	No. of Cases
Fractured navicular bone, recent, without other carpal injury	34
Fractured navicular bone, old, without other carpal injury	26
Fractured navicular bone with other carpal injury	8
Dislocated lunate bone without other carpal injury	8
Dislocated lunate bone with other carpal injury	3
Retrolunar dislocation of capitate bone	6
Fractured lunate bone	5
Kienböck's disease	6
Miscellaneous fractures including chip fractures	11
Cyst of lunate bone	1
Cyst of navicular bone	1
Congenital fusion of triangular and lunate bones	1
	110

to the navicular bone through the second and first metacarpal bones and the second row of the carpus; or the blow may be received directly on the tubercle of the bone. In 2 cases in the series the navicular bone was fractured by a fall which forced the hand sharply into radial deviation and palmar flexion. Given a patient with such a history, with pain in the wrist, which is moderately swollen but without deformity, with tenderness over the "snuff-box" or over the tubercle of the navicular bone, one must strongly suspect injury to this bone. Motions may be only moderately limited, and the usual signs of fracture of a long bone are absent. Roentgenograms taken carefully with the hand in special positions are necessary. Usually the fracture occurs in one of three

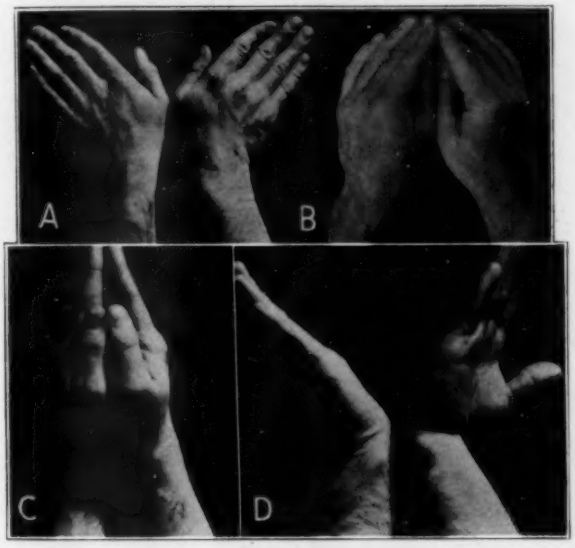


Fig. 9.—Positions of hands for roentgenograms of navicular bone: *A*, ulnar deviation; *B*, midpronation, oblique view; *C*, lateral; *D*, extreme pronation, oblique view.

places (fig. 10), listed here in order of frequency: the central portion, or "waist," of the bone (type 1); the junction of the proximal and the middle third (type 2), and the tubercle of the bone (type 3). To produce fractures of types 1 and 2, the wrist must be forced sharply into dorsiflexion or palmar flexion, with sharp radial deviation. Such a position compresses the navicular bone between the greater multangular bone, the radius and the lunate bone. A fracture of type 3 is sustained when the hand is forced into dorsiflexion and ulnar deviation. In this position the tuberosity is pulled off by its ligamentous attachments. Rarely is the navicular bone fractured by a direct blow; when it is, the

fracture may be comminuted, of type 4 (fig. 11). Occasionally the fracture, although present, may not be demonstrable because of the impaction (case 1). In such a case, if the clinical findings are consistent with a diagnosis of navicular fracture the wrist should be immobilized at once, and further roentgenograms should be made three weeks and possibly six weeks afterward, when the fracture will be demonstrable because of the absorption that always takes place at the fracture line.

TREATMENT OF NAVICULAR FRACTURES

For all fresh fractures of the carpal navicular bone (type 1), for fractures through the midportion (type 2) and for fractures at the

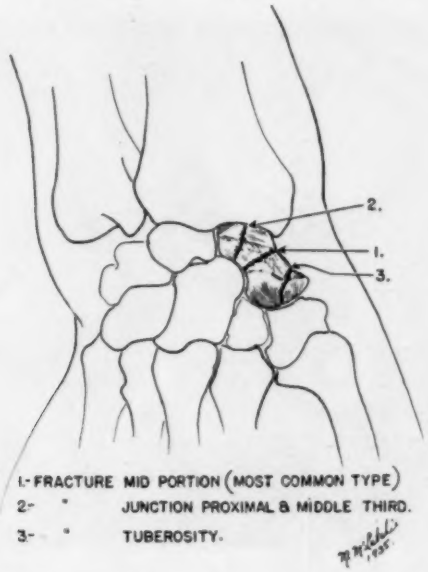


Fig. 10.—Sites of fracture in the navicular bone.

junction of the proximal and the middle third, whether partial or complete, with or without separation of the fragments, early and complete immobilization of the thumb, hand and lower two thirds of the forearm should be carried out (fig. 12). It is ideal to immobilize the thumb completely; the wrist should be in a position of approximately 30 degrees dorsiflexion and 15 degrees radial deviation, since this position approximates the fractured surfaces. The fingers are left free and motion of them is encouraged from the start. Böhler [11] and his colleagues,

11. Böhler, L.: Wien. med. Wchnschr. **85**:803, 1935; The Treatment of Fractures, ed. 4, translated by E. W. H. Groves, Baltimore, William Wood & Company, 1935.

Fig. 11.—Comminuted fracture of the carpal navicular bone. This type of fracture is best treated by primary excision of all fragments. Reduction cannot be effected, and if operation is not done early traumatic arthritis is certain to follow.

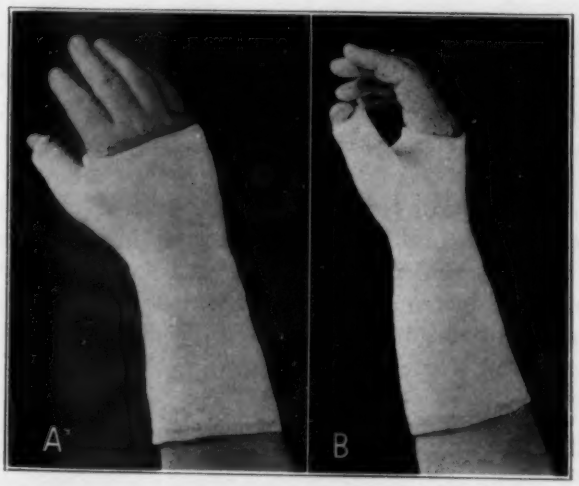


Fig. 12.—Circular plaster splint for immobilization of fractured navicular bone: *A*, anteroposterior view; *B*, lateral view.

Schneck [12] and Watson-Jones [13] have advocated use of the light, nonpadded dorsal splint. I have felt that the circular plaster offers better fixation and is less apt to be disturbed by the use of the hand. The plaster should be worn until union is demonstrable in roentgenograms. Rarely is this union accomplished in less than eight weeks. When union is established it is well to supply the patient with a leather wristlet made from a plaster model, which holds the hand in a position of slight dorsiflexion. It can be worn when the patient is at work and discarded at night. I see no value in physical therapy in this type of fracture. In many of my own cases, I feel sure, it has been harmful, for too much reliance has been placed on increasing the blood supply by heat and massage, and not enough attention has been paid to prolonged immobilization. If necessary, immobilization should be carried out for four months before one admits that the patient has nonunion. If at the end of that time nonunion seems to be definitely established (the diagnosis of this is based entirely on roentgenograms), operative treatment is indicated. Of 34 patients with recent navicular fractures, 12 who were examined at the end of one year or longer had no disability. Yearly end results were not obtained for the remaining 22 patients. Böhler,[11] after experience with 300 recent navicular fractures, stated that all such fractures heal if immobilization is carried out for six weeks. Schneck [12] in his excellent monograph agreed essentially with this point of view. He reported union in 100 per cent of his cases in which the fractures were no more than three weeks old when treatment was started. Haldeman and Soto-Hall [14] secured union by plaster fixation in 75 per cent of 16 recent navicular fractures. Hirsch [15] stated that all fresh navicular fractures unite by bone if they are immobilized for as long as six weeks. Wette [2] recommended immobilization for eight weeks or longer. Speed [16] advocated prolonged immobilization.

Fractures of the tubercle of the navicular bone (type 3) always heal, for a fracture of this kind is largely extra-articular and the blood supply to both fragments is maintained. A fracture of type 4, or the comminuted fracture of the navicular bone, is in all probability best treated by primary excision of the entire navicular bone. To leave the comminuted and displaced fragments to create abnormal friction against the surrounding carpal bones and the radius leads to traumatic arthritis, which is permanent if operation is delayed.

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12. Schneck, F.: Ergebn. d. Chir. u. Orthop. **23**:1, 1930; Zentralbl. f. Chir. **57**:2600, 1930.

13. Watson-Jones, R.: Brit. J. Surg. **22**:63, 1934.

14. Haldeman, K. O., and Soto-Hall, R.: J. Bone & Joint Surg. **16**:822, 1934.

15. Hirsch, M.: Wien. med. Wchnschr. **85**:803, 1935.

16. Speed, K.: J. Bone & Joint Surg. **17**:965, 1935; Surg., Gynec. & Obst. **64**:9, 1937.

OPERATIVE TREATMENT FOR NONUNION OF THE CARPAL NAVICULAR BONE

Excision of One Fragment.—Prior to ten years ago, the accepted form of therapy for nonunion of the carpal navicular bone in most clinics was excision of one fragment of the navicular bone. The end results of such operations left much to be desired.

Excision of the Entire Navicular Bone.—Certain surgeons have advocated the removal of the entire bone as treatment for nonunion. Hirsch [15] reported excellent results in 9 cases following operative removal, with perfect return of function of the wrist and no trace of radial deviation. He advocated early extirpation of the bone before traumatic arthritis in surrounding bones develops. He emphasized the absolute necessity of careful removal of every fragment of the bone and the articular cartilage without damage to the surrounding bones. Operative removal of the entire navicular bone, he said, produces just as good results as does external fixation and in much less time; an excellent return of function may be expected in six weeks. Gurd,[17] of Montreal, is another advocate of excision of the carpal navicular bone for delayed union or for nonunion; he expressed the opinion that it might be an accepted method for primary treatment of navicular fractures. He stated that he had never had cause to regret the removal of either the navicular or the lunate bone, and had been better pleased with the results of this form of operation than with those following either conservative treatment or the use of a bone graft. He would emphasize, he said, the fact that the operation is not easy and that it should be undertaken only by a careful surgeon who knows thoroughly the anatomy of this region. Böhler,[11] on the other hand, stated:

> I have never seen a case in which the usefulness of the hand has returned to normal after removal of the navicular bone. Kemper has collected 60 cases of removal of the navicular and lunate bones; in all of these function of the hand was poor. In cases operated on early the mobility of the wrist may remain good, but the strength of the hand is always weakened.

The only case in our series in which the fracture was treated by excision is reported here (fig. 13):

> CASE 2.—E. deB., a man aged 20, was admitted to the hospital in May 1937. Six months previously he had injured the right wrist while boxing. A splint applied to the wrist by the local physician was worn for one month. The wrist continued to be painful. Examination on admittance showed marked thickening of the wrist in anteroposterior diameter, limitation of flexion, extension, pronation, supination and deviation and tenderness to pressure over the region of the navicular bone. Roentgenograms revealed rotation and subluxation of the navicular bone.

17. Gurd, F. B.: Personal communication to the author.

Operation.—By a dorsoradial approach, the navicular bone was exposed and was found rotated so that the proximal radial articular surface was pointing to the dorsum. There was evidence of an old fracture of this surface, and there were traumatic changes on the articular surface of the radius. Slight posterior displacement of the capitate bone on the lunate bone was also visible. The navicular bone was excised in toto (fig. 13 *C* and *D*). The wound was closed in layers. A light plaster splint was applied to hold the wrist in slight dorsiflexion and ulnar deviation for three weeks.

End Result.—The patient went back to work, and resumed boxing six months after the operation. Two years after the operation he was reexamined; he confessed to some discomfort on the ulnar side of the hand during heavy work. Examination revealed thickening of the wrist. Articular motions were moderately restricted in palmar flexion and radial deviation but practically normal in ulnar deviation and dorsiflexion. The grip of the hand was slightly weakened.

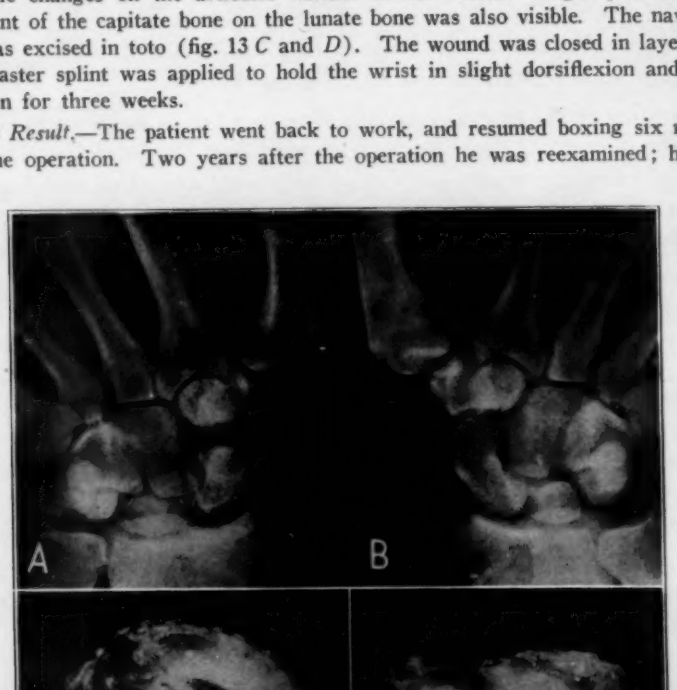

Fig. 13 (case 2).—A navicular fracture which was treated by excision: *A*, the fractured hand, shows the rotation of the navicular bone with depression on the articular surface of the radius; *B*, the opposite (normal) hand; *C* shows the radial articular surface of the navicular bone, which was subluxated, and the cartilaginous surface, which was compressed from the old injury; *D*, articular surface for capitate bone, showing no traumatic change.

The Method of Drilling.—Another method of treatment of the ununited navicular bone has been that of drilling, a method which has

been advocated chiefly by Beck,[18] Speed,[16] Schneck [12] and Steindler.[19] Speed [16] recommended delaying the operation of drilling for six or eight months if adequate external fixation can be maintained during that time. The advocates of this method have suggested that in drilling one should approach the bone through the tabatière and, using a ⅛ inch (0.3 cm.) drill, should make one or more drill holes across the fracture line into the proximal fragment. Speed [16] said that he doubted the necessity of any graft and recommended following the drilling with plaster fixation of the wrist in dorsiflexion and radial deviation.

My experience with drilling has been confined to 3 cases: a case in which the fracture has united by bone; another in which there has been great improvement and there seems to be a strong fibrous union, and a third in which the treatment was a failure, because pain persists and there is marked limitation of motion.

The Autogenous Bone Graft.—The other method of attack on delayed union or nonunion of the navicular bone is that of the autogenous bone graft. The first advocate of this procedure was Adams,[20] who in 1928 demonstrated a case in which bony union had been established by introducing a slot graft from the radius into the navicular bone. Others who have advocated this method are Murray,[21] Burnett,[22] Ethan H. Smith [23] and Allen.[24] This form of treatment has appealed more to my colleagues and me than the other forms described, and we have used it in the majority of the cases in which we have operated. If one considers the reasons for the frequent nonunion of the navicular bone, one must think in terms of blood supply and of the free motion through which the navicular bone normally travels as compared with the other carpal bones. Therefore, the combination of drilling and the introduction of a bone peg offers the best chance of reestablishing blood supply and at the same time of securing fixation of the fragments. In the early cases the graft was placed in a slot on the dorsum of the navicular bone across the fracture line. Recently it has been inserted through the drill hole from the distal to the proximal fragment. Objections to the slot graft are that it is necessary to expose too much of the dorsum of the bone and to interfere with the blood supply to this region; that too much bone is sacrificed from the navicular bone, and that fixation with

18. Beck, cited by Schneck.[12]
19. Steindler, A.: Surg., Gynec. & Obst. **58**:487, 1934.
20. Adams, J. D., and Leonard, R. D.: New England J. Med. **198**:401, 1928.
21. Murray, W. G.: Brit. J. Surg. **22**:63, 1934; Surg., Gynec. & Obst. **60**:540, 1935.
22. Burnett, J. H.: Surg., Gynec. & Obst. **60**:529, 1935.
23. Smith, E. H.: M. Rec. **139**:655, 1934.
24. Allen, A. W.: Personal communication to the author.

the slot graft is not as secure as that with the dowel graft. The advantages of exposing the navicular bone over the dorsum are that the fractured surfaces of the bone can be freshened, that the fragments can be more closely approximated and that the exact position of the graft can be determined. In one of my cases in which the fracture was treated by introducing the graft through the drill hole, the proximal fragment was separated from the distal fragment by the graft and complete bony union was not established although the graft did unite with both fragments (case 15). The likelihood of such a result is a disadvantage of the method of introducing the bone graft through the drill hole.

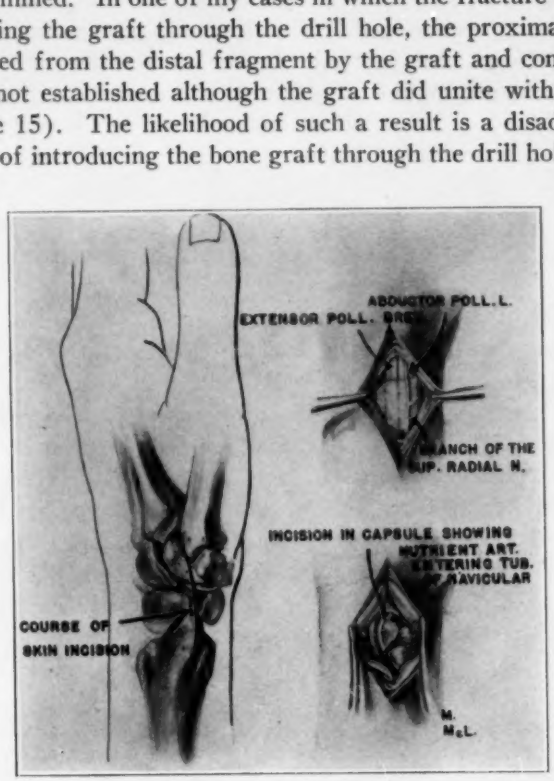
ABDUCTOR POLL. L.
EXTENSOR POLL. BREV.
BRANCH OF THE SUP. RADIAL N.
INCISION IN CAPSULE SHOWING NUTRIENT ART. ENTERING TUB. OF NAVICULAR
COURSE OF SKIN INCISION
M. M.&L.

Fig. 14.—Radial approach to the navicular bone.

Murray,[21] of Toronto, advised exposing the navicular bone through a curved incision over the volar and radial aspects of the wrist (fig. 14), nipping away with a rongeur a small portion of the tubercle of the bone, drilling a large hole through the bone from this point and introducing the graft. With this method Murray has secured bony union in a high percentage of cases. Burnett[22] has also been partial to this method, and through it many of his patients have been rendered free of symptoms, though all the fractures have not united by bone.

At the Massachusetts General Hospital, in 16 cases of nonunion of the navicular bone treatment by the bone grafting operation was applied. End results can be given for only 13 of the cases; for 3, end results cannot be given because the operations were performed too recently. The

average duration of nonunion in these 16 cases was twenty-three months. The operative technic is as follows (fig. 15): A 5 cm. longitudinal incision is made over the dorsum of the wrist midway between the radial styloid process and the dorsal radial prominence. The abductor pollicis longus and the extensor pollicis brevis tendon lie to the radial side of the incision. The extensor carpi radialis longus, the extensor carpi radialis brevis and the abductor pollicis longus tendon are retracted to the ulnar side. The dorsal ligament of the wrist is incised in line with the incision in the skin. The radial articulating surface of the navicular bone comes into view. The ligamentous attachments to the groove of the dorsum of the navicular bone are gently reflected with

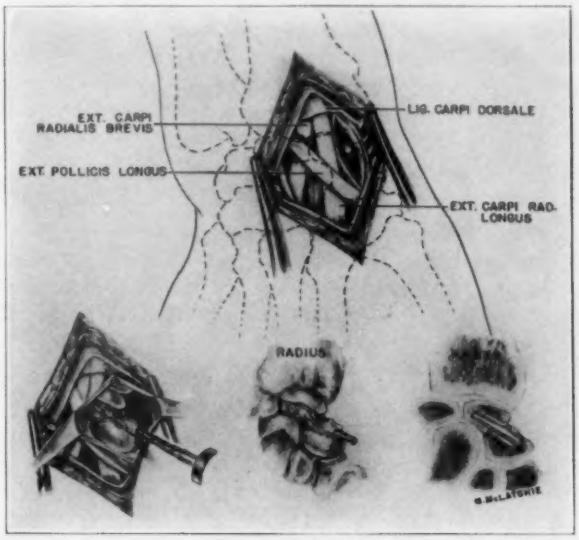

Fig. 15.—Dorsoradial approach to the navicular bone.

sharp dissection until the fracture line is identified. The hand is then placed in ulnar deviation, and with a small spatula between the radius and the navicular bone the proximal fragment is held (fig. 16). A ⅛ inch drill hole is started well out on the distal fragment, as near the tubercle as possible, and continued across the fracture line well into the proximal fragment. The drill is kept about in line with the first metacarpal bone, and the wrist is held in ulnar deviation. When the graft has been removed from the crest of the tibia it is shaped to fit the drill hole and inserted across the fracture line into the proximal fragment. The protruding portion of the graft is nipped off with a rongeur and the dorsal ligament is carefully repaired with fine catgut or silk. The tendons are allowed to fall into place, and the wound is

closed. A plaster casing similar to that previously described is then applied. In general, the period of convalescence is the same as that for fresh fractures of the navicular bone.

There follows a record of each case in which the autogenous bone graft operation has been performed.

REPORT OF CASES

CASE 3.—R. M., a man aged 36, was admitted to the hospital on Feb. 29, 1928. He had fallen on a dorsiflexed hand one year before and had received no treatment. Roentgenograms showed nonunion of the navicular bone. Operation consisted in application of a slot graft from the radius to the navicular bone. The patient reported one year later that he began working five weeks after the operation;

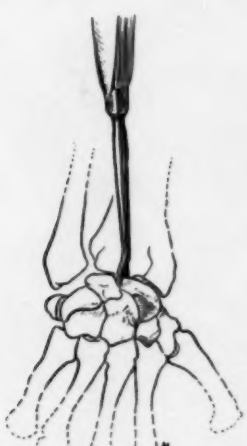

Fig. 16.—Spatula used for holding proximal fragment of navicular bone.

there was no pain and his motions were good. Roentgenograms did not show complete bony union. Examined eight years after the operation, the patient was free of symptoms and was working as a railroad car inspector. Roentgenograms revealed irregularity of the fracture line but no change in the relationship of the fragments in various positions of the hand. There is probably bony union.

CASE 4.—J. B., a man aged 20, was admitted to the hospital on Jan. 14, 1928. He had fallen on an outstretched hand one year and a half before; pain in the wrist had continued, and he had received no treatment. Roentgenograms showed nonunion of the navicular bone. The operation consisted of insertion of a slot graft from the radius. The patient returned to work in four months. Four years later there was slight limitation of motion in dorsiflexion and palmar flexion. Roentgenograms showed the fracture line, and there seemed to be strong fibrous union.

CASE 5.—W. F., a man aged 21, was admitted to the hospital on March 7, 1929. Six months before, he had fallen on the right hand in dorsiflexion and had received

no treatment. Roentgenograms showed the old fracture of the right navicular bone at the junction of the middle and the outer third. The slot graft operation was performed. Postoperative roentgenograms showed one bone fragment in the soft parts. Three months after the operation the patient worked without apparatus. One year later he was free of symptoms, with a normal range of motion. Roentgenograms showed deformity of the navicular bone, with apparent union.

CASE 6.—L. G., a man aged 31, was admitted to the hospital on Jan. 16, 1930. Three months before, in trying to arrest a thief, he had sustained a fracture of the right navicular bone. Roentgenograms showed nonunion of the navicular bone. A slot graft from the tibia was inserted. In two months the patient discarded all apparatus and returned to work. Fifteen months after the operation roentgenograms showed union of the bone through one-half its diameter. The patient was free of symptoms, and his motions were normal.

CASE 7.—J. C., a man aged 26, was admitted to the hospital on May 29, 1930. Eighteen months previously he had fallen on an outstretched hand, sustaining a fracture of the right navicular bone. Roentgenograms showed nonunion. The operation was an insertion of a tibial graft through a drill hole. The patient discarded the apparatus and returned to work in two months. Two and a half years later he was working full time, with the function normal and the fracture line indistinct. The case is not classed as one of definite bony union.

CASE 8.—J. H., a man aged 30, was admitted to the hospital in 1930. Five months previously he had fallen on an outstretched hand, sustaining a fracture of the right navicular bone. Roentgenograms showed nonunion. A slot graft from the tibia was inserted. The patient discarded all apparatus and returned to work six weeks after the operation. Two years later there was bony union. The patient was working full time at his old job, and function was normal.

CASE 9.—M. B., a man aged 28, was admitted to the hospital in 1930. He had fallen on an outstretched hand four months previously, receiving a fracture of the right navicular bone. He had been given no treatment. Roentgenograms showed nonunion. A slot graft from the tibia was inserted. The patient returned to work in six weeks without apparatus. He left the country but wrote two years later that so far as he could determine his hand was absolutely normal.

CASE 10.—P. D., a man aged 21, was admitted to the hospital on July 11, 1934. He had fallen on an outstretched hand nine months previously and had received no treatment. Roentgenograms showed a fracture of the right navicular bone at the junction of the outer and the middle third. A bone graft from the tibia was inserted through a drill hole. The patient wore a plaster casing for eight weeks and a leather wristlet for an additional eight weeks. At the end of eight months there were still pain and some limitation of motion. Roentgenograms showed nonunion.

CASE 11.—K. K., a man aged 27, was admitted to the hospital on Feb. 17, 1931. He had fallen on an outstreatched hand sixteen months previously and had received no treatment. Roentgenograms showed the old fracture of the right navicular bone at the junction of the middle and the outer third. A bone graft from the tibia was countersunk into the navicular bone. At the end of four years the patient was working normally without pain. His motions were normal. Roentgenograms showed some evidence of union, but it was not solid.

CASE 12.—J. P., a man aged 21, was admitted to the hospital in January 1935. Two months before, he had fallen on an outstretched hand. He had received no treatment. There were still pain and weakness of the wrist. Roentgenograms showed fibrous union. A bone graft from the tibia was inserted through a drill hole. The patient wore a circular plaster for one month and a leather wristlet for an additional two months. Five months later roentgenograms showed bony union.

Fig. 17 (case 13).—Bony union produced by autogenous graft in an eight year old fracture of the navicular bone: *A*, the wrist eight years after original injury; *B*, the wrist two years after autogenous graft, showing bony union, although there is still some vacuolation of the fragments.

CASE 13.—F. D., a man aged 27, was admitted to the hospital in September 1935. He had fallen on an outstretched hand eight years previously and had received no treatment. Roentgenograms showed nonunion of the navicular bone with cystic degeneration. A bone graft from the tibia was inserted through a drill hole. Two years later the patient stated he was working full time in a machine shop in New

Jersey. There seemed to be "more bone" in the wrist, but it was stronger and there was very little pain. Motions were about two-thirds normal. Roentgenograms showed bony union (fig. 17).

CASE 14.—W. K., a man aged 26, was admitted to the hospital in September 1934. He had fallen on a dorsiflexed hand six years previously while playing football. The wrist had been painful at intervals since the original injury. After a second fall, one year before admission, the pain increased. Roentgenograms showed nonunion of the navicular bone. A bone graft from the tibia was inserted through a drill hole. Six months later roentgenograms showed nonunion, with absorption of the graft. The patient is still wearing a wristlet. This case must be listed as a failure.

CASE 15.—R. T., a man aged 19, was admitted to the hospital on Feb. 24, 1936. Six months before, the patient had injured his wrist while playing football. The injury was regarded as a sprain, and roentgenograms showed "no fracture." The pain had continued, and three months before admission the patient had been given a leather wristlet, which he wore intermittently. Roentgenograms showed a distinct fracture line with delayed union. The wristlet was not helpful. Roentgenograms on admission showed the old fracture at the junction of the proximal and the middle third, with nonunion. A bone graft from the tibia was inserted through a hole drilled through the distal and the proximal fragment. Postoperative roentgenograms showed the fragments in good position and the graft in a satisfactory position, although the graft extended slightly beyond the proximal portion of the navicular bone. There was bony union through the region of the graft. The patient was examined at the end of seventeen months. There were still thickening of the navicular bone and restriction of motion of the wrist to approximately two-thirds normal. There was occasional pain in the wrist when the patient struck a sudden blow. Roentgenograms showed union at the site of the graft but no evidence of union of the main portion of the fragments.

COMMENT

One fracture, that in case 14, was not improved by the operation; in this instance there was nonunion of six years. Possibly this fracture would have been better treated with excision of the entire navicular bone. In 2 cases, 10 and 15, there was only moderate improvement. The injured wrists in these 2 cases continued to have fairly marked limitation of motion, and pain when the wrist was forced to the limit of motion. In case 13 bony union was secured after eight years of nonunion. In another case the patient was free of symptoms and had a normal range of motion but the complete fracture line could be seen when the last roentgenograms were taken. In the remaining 8 cases either partial or complete bony union was produced and the patient was relieved as a result of the operation.

SUMMARY

An adequate knowledge of the relationship of the carpal bones is necessary for making accurate diagnoses of injuries to these structures. The importance of early diagnosis and adequate early treatment of carpal

navicular injuries is emphasized. Practically all navicular fractures heal if recognized and treated early by prolonged immobilization. For fractures in which nonunion of the navicular bone has developed as a result of delayed treatment, the introduction of an autogenous bone graft introduced through a drill hole in the bone followed by prolonged fixation in plaster seems to produce the most satisfactory results.

ABERRANT ADRENAL TUMOR OF UPPER PART OF ABDOMEN

REPORT OF A CASE WITH SIX YEAR CURE

STUART F. MACMILLAN, M.D.
AND
JUDSON B. GILBERT, M.D.
SCHENECTADY, N. Y.

The following case is reported because of the unusual location of a large ectopic adrenal tumor and its successful surgical removal. Mention is made of similarly located tumors, and the early history of aberrant adrenal tissue in general is briefly given. Much of the literature concerning this subject is confusing because of the lack of proper classification. Frequently no clear distinction is made between malignant and benign nodules of adrenal tissue. The frankly malignant tumors of such origin are rare.

REPORT OF CASE

Clinical History.—E. R., a white married woman aged 51, was admitted to Ellis Hospital on March 29, 1933, with the chief complaint of intermittent attacks of nausea and vomiting. The family history seemed irrelevant except that the father had died of carcinoma of the colon at the age of 68.

The illness for which the patient sought relief had begun one year before admission, with an attack of nausea and vomiting. This attack was followed by similar attacks, coming in the beginning about once a month and then increasing in frequency. The duration of the attacks was short at first, but later in the illness they persisted for two or three days. The patient complained of a feeling of fulness and pressure in the epigastrium but had no pain. There was moderate constipation, but the stools were of normal color. There was slight loss of weight, and the appetite was poor. In the latter part of the illness the patient became aware of a mass in the upper part of the abdomen.

In 1924 roentgen therapy was given for uterine bleeding (2 milliampere hours in divided doses), and menses ceased thereafter. In 1929 the patient complained of frequency of urination and a bearing-down sensation. Repeated urinalyses showed the urine normal, and the symptoms were promptly controlled by medication.

Physical Examination.—The patient was well developed and fairly well nourished. The skin showed moderate pallor. The pulse, temperature and respirations were normal. Examination of the heart and lungs disclosed nothing unusual. The blood pressure was 140 systolic and 80 diastolic. The abdomen was soft and

From the Surgical Service, Ellis Hospital.

not distended. There was a freely movable firm rounded mass in the upper and middle portion of the abdomen, slightly tender and about the size of a large orange. The liver and spleen were not palpable, and pelvic and rectal examinations gave negative results. There was no evidence of any secondary sexual changes suggesting virilism.

A roentgen examination of the stomach and small intestine disclosed no abnormality except decided iliac stasis. The colon showed no filling defects, but there was rapid emptying of the cecum. The abdominal mass appeared to be outside the gastrointestinal tract.

Laboratory Data.—Three specimens of urine examined before operation were free of albumin and sugar and contained no red blood cells or leukocytes. A fourth

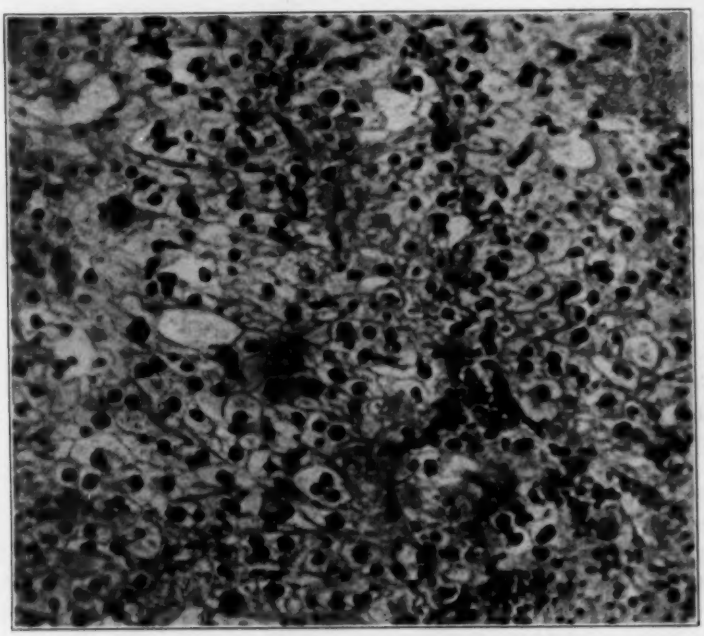

Fig. 1.—Aberrant adrenal carcinoma (low power).

specimen examined before operation was likewise free of albumin and sugar but contained a few red cells and white cells. A blood count revealed hemoglobin 61 per cent (Newcomer); red cells, 3,320,000, and white cells, 7,000, with polymorphonuclears 62 per cent, lymphocytes 28 per cent, endothelial leukocytes 5 per cent, eosinophils 3 per cent and basophils 2 per cent. The red blood cells were normal in size and shape. The urea nitrogen content of the blood was 9.5 mg. and the sugar content 93.7 mg. per hundred cubic centimeters. The Wassermann reaction of the blood was negative.

Operation and Course.—After a preliminary blood transfusion an operation was performed on April 3, 1933, with the patient under spinal anesthesia. An upper right rectus incision disclosed a nodular mass approximately 6 by 10 cm. in the

omentum just beneath and adherent to the middle of the transverse colon. The liver, the pouch of Douglas and the mesenteric lymph glands contained no nodules suggesting metastasis. The rest of the colon was normal. An attempt was made to separate the mass in the omentum from the transverse colon but had to be abandoned because of the danger of spilling the soft contents of the tumor. Instead, the tumor and the adherent portion of the colon were resected in one piece. The divided ends of the bowel were inverted and a lateral anastomosis was performed. The cecum, which was very mobile, was then sutured to the peritoneum at the lower angle of the wound; a potential cecostomy opening was thus established.

Three days after the operation it was necessary to open the cecum with a cautery to relieve distention and vomiting. On the fourth postoperative day fluids

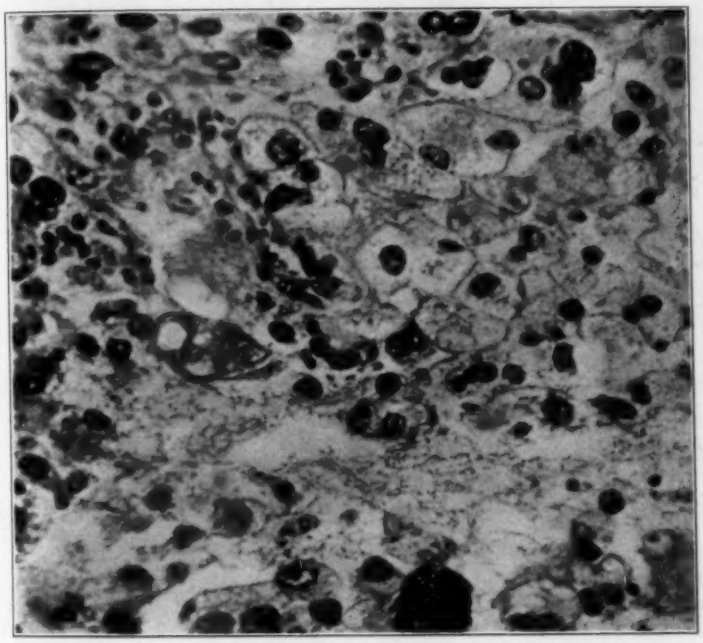

Fig. 2.—Aberrant adrenal carcinoma (high power).

were taken by mouth, and the postoperative course was uneventful thereafter. The patient was discharged fifteen days after the operation, with the operative wound healed and the cecostomy wound closing rapidly.

The tumor was an irregular globular mass measuring 6 by 7 by 10 cm. Its outer surface was nodular, capsulated and covered in part with small fat lobules. Several bluish nodules of tissue were seen beneath the serous surface. On section the mass appeared to be composed mainly of soft yellowish hemorrhagic tissue without definite structure. A narrow margin of grayish soft translucent tissue was found beneath the capsule. The piece of attached intestine, 4.5 cm. long, was without evidence of tumor, and the mucosa was intact. Microscopic sections showed islands of tumor tissue surrounded by extensive areas of necrosis. The tumor cells

were large and somewhat polygonal and were best preserved about the vascular spaces. The cytoplasm was markedly granular or cribriform. Nuclei varied greatly in size, but the majority were large and rather pale, and mitotic figures were present. A diagnosis of hypernephroma (adrenal carcinoma) was made.

The patient has been in good health since operation. Repeated physical examinations and urinalyses have failed to show any evidence of recurrence.

LITERATURE

The terminology of ectopic, or misplaced, adrenal rests and of subsequently developing tumor has been a subject of much speculation since the work of Chiari [1] in 1884. Such tissue has been described by names like heterotropic hypernephroma, aberrant adrenals of Marchand and extrarenal hypernephroma.

The earliest descriptions were by Rokitansky [2] in 1849, by Marchand [3] in 1878, and by Chiari six years later. Apparently Chiari was the first to describe malignant transformation of such ectopic tissue located in the retroperitoneal space. Such adrenal rests have been described throughout the upper part of the abdomen, below the diaphragm and in the retroperitoneal space as low as the small pelvis in females and the scrotum in males. The embryologic development of these aberrant adrenal rests was thoroughly described by Broman [4] in 1911. Glynn [5] added materially to the subject in 1912, and made an even fuller study in 1921.

Nicholson [6] in 1894 described an ectopic adrenal tumor found at autopsy, closely similar to the tumor in the case which we have reported. The mass measured 1.5 by 0.25 inches and was attached to the transverse mesocolon, the pancreas lying behind and above and the transverse colon in front. Microscopically this tumor proved to be an adrenal capsule. Evidently this tumor was found accidentally and was not malignant.

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1. Chiari, H.: Zur Kenntnis der accessorischen Nebennieren des Menschen, Ztschr. f. Heilk. **5**:449-458, 1884.

2. von Rokitansky, C.: A Manual of Pathological Anatomy, translated by E. Sieveking, London, Sydenham Society, 1849, vol. 2, p. 244.

3. Marchand, F.: Ueber accessorische Nebennieren im Ligamentum latum, Virchows Arch. f. path. Anat. **92**:11-19, 1883.

4. Broman, I.: Normale und abnormale Entwicklung des Menschen, Wiesbaden, J. F. Bergmann, 1911, p. 808.

5. Glynn, E. E.: (*a*) The Adrenal Cortex, Its Rests and Tumors: Its Relation to Other Ductless Glands and Especially to Sex, Quart. J. Med. **5**:57-192, 1912; (*b*) A Comparison Between Ovarian "Hypernephroma" and Luteoma and Suprarenal Hypernephroma, with Comments on Suprarenal Virilism, J. Obst. & Gynaec. Brit. Emp. **28**:23-68, 1921.

6. Nicholson, B. S.: Abnormal Position of Suprarenal Gland, Brit. M. J. **1**:408, 1894.

Gynecologists, especially Glynn, have described such tumors in the small pelvis and the ovary. Schiffmann in 1926 [7] and in 1930 [8] reported tumors arising in the female pelvis, the second of which invaded the mesentery. He described the case of a 78 year old woman who complained of abdominal pain of two weeks' duration. A tumor the size of a head filled the right side of the pelvis and displaced a small uterus to the left lower quadrant of the abdomen. A diagnosis of intraligamentary tumor was made. Operation disclosed a retroperitoneal tumor 11 by 12 by 16 cm., the upper pole of which protruded into the mesenteric root of the cecum. The patient died three days later of cardiac insufficiency, and necropsy revealed a hypernephroid tumor of the lower pole of the left kidney which infiltrated the renal vein. The foregoing case illustrates a fairly frequent condition in which the secondary tumor is obvious and the seemingly primary tumor obscure. It is of interest that the upper pole of the pelvic tumor invaded the mesentery of the large bowel.

An unusual case of adrenal virilism was described by Kolodny [9] in 1934. A 37 year old woman noted a mass in the left epigastrium about twelve months before examination. The tumor grew rapidly and was associated with digestive difficulty. Menstruation had ceased about eight months before discovery of the tumor. Examination disclosed a rather obese woman with coarse voice and features and with rough, red skin. The distribution of the suprapubic hair was of definitely vertical (male) type. The clitoris was twice the normal size. A tumor the size of a child's head was located in the left side of the epigastrium. Operation disclosed the tumor adherent to the abdominal wall, with the transverse colon tightly stretched over the inferior and the posterior aspect. The tumor, which weighed 1,250 Gm., was located between the leaves of the transverse mesocolon in the region of the solar plexus. The tumor was removed, and because of invasion of the stomach a Billroth I resection was necessary. The sexual changes retrogressed after operation. Six months after operation roentgenograms of the chest disclosed pulmonary metastasis, and one month later, or seven months after the operation, the patient died.

SUMMARY

An unusual case of aberrant adrenal tumor in the upper part of the abdomen of a 51 year old woman which was successfully removed over six years ago is reported.

7. Schiffmann, J., and Szamek, L.: Ein hypernephroides Sarkom im kleinen Becken, Arch. f. Gynäk. **127**:194-207, 1926.

8. Schiffmann, J.: Hypernephroides Sarkom im Beckenbindegewebe; hypernephroides Sarkom der Niere, Arch. f. Gynäk. **144**:685-702, 1930.

9. Kolodny, A.: Suprarenal Virilism in a Woman: Tumor of an Extrarenal Suprarenal Rest, J. A. M. A. **102**:925-926 (March 24) 1934.

Three cases are cited from the literature in which invasion of the mesentery occurred, in 2 of which cases the tumor was located in the upper part of the abdomen.

NOTE.—Attention should be called to the recent excellent article of Nelson.[10]

Dr. Charles G. McMullen permitted us to report the case, and Dr. Ellis Kellert supplied the photomicrographs.

10. Nelson, A. A.: Accessory Adrenal Cortical Tissue, Arch. Path. **27**:955-965 (June) 1939.

CARCINOMA OF THE RECTUM AND OF THE RECTOSIGMOID IN THE YOUNG

CHARLES W. MAYO, M.D.
AND
GORDON F. MADDING, M.D.
Fellow in Surgery, the Mayo Foundation
ROCHESTER, MINN.

The factors which influence the prognosis of carcinoma of the rectum and of the rectosigmoid in persons 30 years of age and less are multiple, although at present the most satisfactory indicators are the ability of the patient to withstand the effects of surgical removal of the lesion and the presence or absence of metastasis. The latter factor closely parallels the grade of the tumor as classified by Broders.[1] The clinical observations, the age and the sex of the patient and the rectal and proctoscopic observations, as well as the observations made at the time of surgical exploration, all must be correlated before the future health of a patient can be determined with any approximation of accuracy.

The present paper is a review of 116 cases of carcinoma of the rectum and of the rectosigmoid in which persons 30 years of age and less were involved. The patients were examined at the Mayo Clinic between the years 1910 and 1933, inclusive. Although the number of instances of this type of lesion seen annually since 1933 has increased, it was necessary for the purposes of this study to exclude all cases recorded at the clinic after 1933 so that a five year survival rate might be determined. It is of interest to notice that 3.4 per cent of the patients with carcinoma of the rectum and rectosigmoid who were treated at the Mayo Clinic between the years 1910 and 1933 inclusive were 30 years of age or younger. Phillips and Walters [2] recently reviewed the cases of carcinoma of the stomach at the Mayo Clinic in which the patients were 30 years of age or younger and found this group to constitute 2.4 per cent of the total number of patients with carcinoma of this organ.

In computing the statistics concerning patients who were operated on, we did not include in our calculations any patient who had not been traced for a period considered by us to be sufficient for the estimation

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From the Division of Surgery, the Mayo Clinic.

1. Broders, A. C.: The Grading of Carcinoma, Minnesota Med. **8**:726-730 (Dec.) 1925.

2. Phillips, R. B., and Walters, W.: Personal communication to the authors.

of legitimate survival rates. Of the cases in which death occurred in the hospital and in which death was designated as "operative" or "hospital," none was included in computing the survival rate.

The part that clinical observations play in determining the curability of a lesion is not great, but when on rectal and proctoscopic examination a carcinoma has been found the prognosis depends on the operability of the lesion, which, in turn, depends on the grade of the lesion and the general condition of the patient. Age is another factor which influences the prognosis. Although the lesions of the young persons in our series were found to be of a higher grade than is usual among older patients, we did not find justification for the hopeless outlook taken by some authors for this group of patients. Young patients, as a rule, withstand surgical procedures well. Because of this, the percentage of young patients who are acceptable for radical operative procedures is greater than that of older patients who are acceptable for the same procedures. In 56 per cent of the cases studied, some form of resection of the lesion had been performed as a curative procedure and not for palliation.

It is generally believed that the operative risk accompanying resection of the rectum is less among females than among males, largely because the width of the female pelvis is greater than that of a male, a fact which renders mobilization of the female rectum easier and, in consequence, lessens the risk of sepsis. In this study, all patients in whom anterior resection of rectal lesions was undertaken were women. This accounts in a large measure for the higher operative mortality rate among women. The numbers of patients of the two sexes were about equal, 51 per cent of the patients being males and 49 per cent being females. Ninety per cent of the "hospital deaths" in the group of cases in which resection was performed occurred among women.

Rectal and proctoscopic examinations made diagnosis possible in 100 per cent of the cases in this study. In addition to permitting a diagnosis of carcinoma, examinations enabled other factors to be learned which aided in formulating a prognosis. As a rule, the smaller, the more protuberant and the more movable the lesion, the more likely it is that satisfactory and complete resection may be performed, although Gilchrist and David,[3] after analysis of 22 specimens, concluded that the size of the tumor is of little value in determining the presence or absence of metastasis to lymph nodes. Tumors which are questionably operable because of their size may not involve lymph nodes, and, conversely, small tumors may show extensive involvement of lymph nodes. There is one type of carcinoma of the rectum which is recognizable grossly and which usually is of a low grade of malignancy and unlikely to

3. Gilchrist, R. K., and David, V. C.: Lymphatic Spread of Carcinoma of the Rectum, Ann. Surg. **108**:621-642 (Oct.) 1938.

metastasize; this is the "papilliferous carcinoma," classed as the type of growth which protrudes into the lumen of the rectum. The aforementioned qualities characterizing this lesion were found to be present among those patients in our series who had the lesion and are also observations which have been noted by Dukes,[4] McVay[5] and Hayes.[6] Lesions situated anteriorly in the rectum, particularly perforating lesions, have a poorer prognosis than have similar lesions situated on the posterior rectal wall, for the reason that such anterior lesions commonly involve other viscera. Removal of lesions of the anterior rectal wall entails added risk. Gilchrist and David found more lesions with metastasis among those situated on the mesenteric border of the bowel than among those arising on the antimesenteric border. Westhues[7] has pointed out that fixation to the sacrum or to the prostate gland is caused more often by inflammatory reaction than by the carcinoma itself, and his conclusion should be considered before a tumor with such fixation is called "inoperable."

The situation of the tumor is of importance from the standpoint of prognosis, because of the difference caused by it in the time of appearance of symptoms, the grade of the tumor and the channels by means of which metastasis occurs. Tumors situated near the external anal orifice usually are epitheliomatous and for the most part follow the lymphatic vessels which drain toward the inguinal glands. When these are involved, the lesion is rendered inoperable by anything other than a palliative procedure. Low-lying lesions may have high metastases, as has been shown by Gilchrist and David, and such metastases usually follow the lymphatic chain along the superior hemorrhoidal artery. Because of this, high ligation of the artery and the accompanying lymphatic vessels should be carried out when possible. When the lesion is situated in the lower or the middle third of the rectum, a sufficiently accurate estimate of its mobility can be made by the examining finger. When the lesion is situated higher than the aforementioned structures, particularly when it is in the rectosigmoid region, the accuracy of determining its operability is practically nil.

The advisability of attempting to determine the degree of fixation and situation of the lesion by manual and proctoscopic examination has been questioned, and justifiably so. Rectosigmoid growths often

4. Dukes, C. E.: The Classification of Cancer of the Rectum, J. Path. & Bact. **35**:323-332, 1932.

5. McVay, J. R.: Involvement of the Lymph-Nodes in Carcinoma of the Rectum, Ann. Surg. **76**:755-767 (Dec.) 1922.

6. Hayes, J. M.: The Involvement of the Lymph Glands in Carcinoma of the Large Intestine, Minnesota Med. **4**:653-663 (Nov.) 1921.

7. Westhues, H.: Die pathologisch-anatomischen Grundlagen der Chirurgie des Rektumkarzinoms, Leipzig, Georg Thieme, 1934.

telescope themselves into the lower part of the rectum and physically appear to be fixed, but on exploration the lesion will be found to be freely movable and situated at a much higher level. In the present study, 28 per cent of the resected lesions had been described as "fixed" on proctoscopic and manual examination, 34 per cent had been recorded as being attached or having limited motion and 38 per cent had been recorded as freely movable. Among younger persons as well as the older group, lesions situated high in the rectum or rectosigmoid had a poorer prognosis from the standpoint of operability, because they usually required some type of combined abdominoperineal resection or anterior resection, both of which procedures carry a higher operative risk than does posterior resection. In addition to the higher operative mortality in cases of high-lying tumors, the duration of life in these instances also was decreased. The average duration of life in cases in which resection was performed for lesions of grade 2 or grade 3 situated in the upper third of the rectum or in the rectosigmoid was three and two-tenths years. The average duration of life in a similar group of cases in which the lesions were situated in the lower third of the rectum was five and eight-tenths years. In neither group were deaths in the hospital included in the calculations.

The prognosis based on exploratory laparotomy was, generally speaking, more nearly accurate than that based on clinical examination and proctoscopic observations. This increase in accuracy was most noteworthy in cases of high-lying lesions, particularly in patients having a small pelvis. The mobility of the tumor, the presence or absence of regional and visceral metastasis and the presence of free fluid in the abdomen all provide valuable information as to operability of the lesion.

Although gross examination of the lymph nodes at the time of exploration may be used as a rough guide to operability, it should not be the determining factor as to whether a curative or a palliative procedure should be performed. Some of the largest glands removed at the time of exploration were found on histologic examination to be inflammatory. Gabriel, Dukes and Bussey,[8] on examining 1,242 lymph nodes, made a study as to the accuracy of gross examination of the nodes. Of 1,242 nodes, the appearance of 905 was considered on the basis of gross characteristics to be normal, but subsequent microscopic examination showed 18 to contain metastasis, an error of 2 per cent. Of 337 nodes of which the appearance was judged to indicate malignant involvement on the basis of gross characteristics, metastasis was present in only 132—an error for 265, or 61 per cent, of the total number of nodes. The commonest error in our cases was that of presuming nodes to be

8. Gabriel, W. B.; Dukes, C., and Bussey, H. J. R.: Lymphatic Spread in Cancer of the Rectum, Brit. J. Surg. **23**:395-413 (Oct.) 1935.

involved by metastasis when in reality the enlargement was due to inflammatory involvement. Although the prognosis when involvement of the nodes is present is, as a rule, poorer than when it is absent, our study showed that a certain proportion of patients do survive the five year period and that, although a more radical operation may be necessary, something more than a palliative procedure should be instituted. Of the patients for whom resection was performed, 62 per cent were found by histologic examination to have nodular involvement. Brown and Warren [9] found the lymph nodes to be disappointing indicators as to prognosis for carcinoma of the rectum, because visceral metastasis often occurs independently of neoplastic lymph nodes. It would appear that local growth often provides a clue as to the possibility of visceral metastasis, since evidence of invasion of the blood vessels was noted on histologic examination of several of our patients. It is well to remember, however, that many such instances were encountered in which no evidence of visceral metastasis was noted. Warren and Gates [10] have shown experimentally that only a small proportion of tumor cells entering the blood stream become manifest as visceral metastasis. Clute and Warren [11] have shown the same thing concerning the thyroid gland, in which intravascular invasion of a malignant lesion frequently is noted but in which distant metastasis rarely is seen.

PROGNOSIS BASED ON PATHOLOGIC INVESTIGATION

Carcinoma of the rectum may be subdivided into numerous gross forms, such as polypoid carcinoma and mucoid papillary carcinoma, but this is often misleading. Broders [12] stated that such a classification is unnecessary and confusing and chose to classify the forms under the general term "adenocarcinoma."

The tumors of this series were graded as suggested by Broders because the value of this method of grading has been demonstrated on numerous occasions (table 1).

Of the patients with grade 1 carcinoma subjected to some form of curative operation, 75 per cent survived the five year period. There was a decrease of 28 per cent for the next grade, and only 10 per cent of the pateints with grade 3 tumors survived the five year period. As the grade of malignancy increased, the percentage of five year cures decreased.

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9. Brown, C. E., and Warren, S.: Visceral Metastasis from Rectal Carcinoma, Surg., Gynec. & Obst. **66**:611-621 (March) 1938.

10. Warren, S., and Gates, O.: The Fate of Intravenously Injected Tumor Cells, Am. J. Cancer **27**:485-492 (July) 1936.

11. Clute, H. M., and Warren, S.: Cancer of the Thyroid Gland, Am. J. Cancer **15**:2563-2582 (Oct.) 1931.

12. Broders, A. C., cited by Buie,[14] p. 378.

The data in table 2 are in agreement with those of other reports [13] which support the contention that carcinoma in young persons is usually of a higher grade than in older persons. We encountered 1 case at the clinic, however, in which a child 2½ years of age had a large bleeding polyp situated in the upper third of the rectum. This polyp was found to be an adenocarcinoma of grade 1. The lesion was fulgurated, and the patient was living and well nine years later (table 2).

TABLE 1.—*Cases in Which Operations for Cure Were Performed: Grades of Tumors, Percentages of Cases in Each Grade and Percentage of Five Year Survivals*

Grade (Broders)	Percentage of Cases	Percentage of Survival
1	12.0	75
2	50.0	47
3	30.9	10
4	7.1	*

* One patient lived fifteen years. The other patients died within an average of eight months after the operation. Cases of "operative death" or death in the hospital are not included.

TABLE 2.—*Grades of Lesions and Percentage of Cases of Each in a Total Group of 116 Cases of Carcinoma of the Rectum and Rectosigmoid in Patients Under 30 Years of Age*

Grade (Broders)	Percentage
1	11.7
2	46.7
3	26.6
4	15.0

TABLE 3.—*Grades of Tumor: 2,723 Cases of Carcinoma of the Rectum in Persons of All Age Groups* *

Grade (Broders)	Percentage of Cases
1	45
2	39
3	15
4	1

* As studied by L. A. Buie.

Table 3 represents the findings of Buie,[14] who reviewed 2,713 cases of carcinoma of the rectum involving patients of all ages; carcinoma had

13. Brindley, G. V.: Carcinoma of the Rectum: Factors Affecting Its Cure, J. A. M. A. **108**:37-43 (Jan. 2) 1937. Shedden, W. M.: Carcinoma of the Rectum and Sigmoid with Particular Reference to the Disease as Seen in Youth, New England J. Med. **209**:528-539 (Sept.) 1933. Fowler, L. H.: Malignant Epithelial Neoplasms, Carcinoma and Epithelioma, Occurring in Persons Under Twenty-Six Years of Age, Surg., Gynec. & Obst. **43**:73-84 (July) 1926.

14. Buie, L. A.: Practical Proctology, Philadelphia, W. B. Saunders Company, 1937.

been diagnosed on proctoscopic examination and had been confirmed by histologic means. It will be noted that a greater percentage of high grade tumors occurs in patients under 30 years of age than in older patients. By comparing tables 2 and 3, one sees that among persons less than 30 years of age a greater percentage of the lesions are of grades 2 and 3, whereas in the group which includes all ages, represented in table 3, a greater percentage of the lesions are of grades 1 and 2 than of the other two grades.

The type of surgical procedure employed not only affects the immediate mortality (hospital mortality) but in a measure determines the curability of the patient. The type of operation to be employed rests on an analysis of a number of factors, namely, the age of the patient, the situation and grade of the lesion, the duration of symptoms and the general condition of the patient. A young patient is fortunate from every standpoint if the lesion is situated low in the rectum. In the analysis of the present series of cases, patients with lesions situated low in the rectum for which some form of posterior resection was performed were found to have an average postoperative life of five and eight-tenths years, with an operative mortality of only 2.7 per cent. The combined operative mortality for the entire group of patients treated by resection was 12.3 per cent.

SUMMARY AND CONCLUSIONS

A series of 116 cases of carcinoma of the rectum and of the rectosigmoid in persons 30 years of age and less, observed from 1910 to 1933 inclusive, was studied.

Lesions situated high in the rectum or rectosigmoid have a poorer prognosis from the standpoint of operability as well as from the standpoint of duration of life.

The prognosis based on exploratory laparotomy is superior to that based on clinical examination.

The grade of the tumor as determined by Broders' classification and the presence or absence of local or visceral metastasis are the most important aids in establishing an accurate prognosis. The incidence of visceral and local metastases closely parallels the grade of the original lesion.

ANKLE FUSION FOR CORRECTION OF PARALYTIC DROP FOOT AND CALCANEUS DEFORMITIES

BYRON B. KING, M.D.*
NEW YORK

Recent reports have been published concerning the treatment of paralytic drop foot by means of posterior bone block operations. Admittedly, an appreciable percentage of unsatisfactory results has followed the use of this procedure.[1] Posterior bone block for paralytic drop foot was tried at the New York Orthopaedic Dispensary and Hospital, but the results were not satisfactory. Accordingly, the procedure was abandoned. Ankle fusion was adopted and has been used extensively for both drop foot and calcaneus deformities.

During the five year period from 1934 to 1938 inclusive 106 ankle fusions were done in this hospital for the correction of paralytic deformities resulting from anterior poliomyelitis. Ankle fusion was done in 72 instances to correct drop foot deformity and in 34 instances to correct calcaneus deformity. The patients have been observed from year to year in the follow-up clinic, and the end results have been gratifying.

DROP FOOT

Among the 72 patients in whom ankle fusion was done to correct drop foot deformity, there were 52 females and 19 males. Their ages at operation ranged from 8 to 39 years, the majority being in the second decade. In 66 instances a subtalar triple arthrodesis had been done previously because of concurrent lateral instability of the foot caused by varus or valgus deformity. The involved extremities presented from ¼ to 2½ inches (0.64 to 6.2 cm.) of shortening; in 3 instances the leg was ¼ inch (0.64 cm.) longer than its fellow.

Twenty-three patients with a paralytic drop foot also had an unstable knee because of partial or complete paralysis of the quadriceps femoris muscle. After ankle fusion with the foot in the proper degree of equinus, 19 of the 23 knees were stabilized so that no external support (in the form of the hand held over the knee or a long leg brace) was necessary. Two of the 4 patients in whom the knee was not stabilized after ankle fusion presented marked relaxation and recurvation at the involved knee and will require knee fusion for stabilization. In a case

* Annie C. Kane Fellow, New York Orthopaedic Dispensary and Hospital.

1. Carrell, W. B., and Childress, H. M.: Posterior Bone Block in Talipes Equinus: Some Factors Determining the End-Results, South. M. J. **32**:528 (May) 1939.

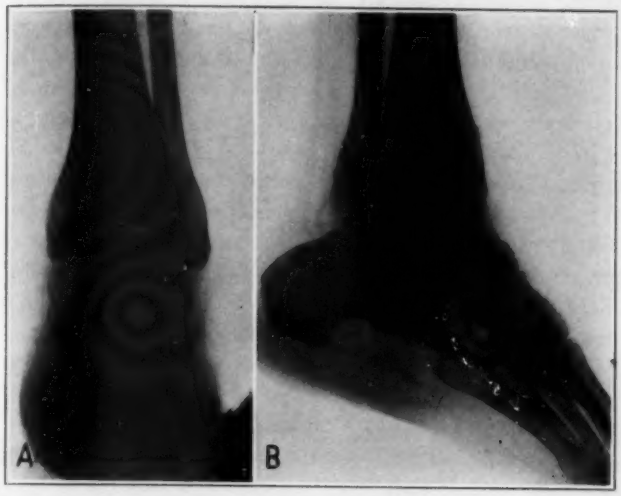

Fig. 1.—Preoperative anteroposterior views of a drop foot deformity due to anterior poliomyelitis. *A*, anteroposterior view; *B*, lateral view. A subtalar triple arthrodesis had been performed previously.

Fig. 2.—*A*, anteroposterior view and *B*, lateral view of the ankle shown in figure 1, twelve weeks after ankle fusion. The ankle was solidly fused at 99 degrees of dorsiflexion.

of drop foot with associated instability of the knee, it is wise to make a preoperative decision whether ankle fusion will successfully stabilize the knee; this is true also of an instability of the knee associated with calcaneus. To determine this, a short leg plaster walking cast is applied with the foot in approximately 10 degrees of equinus. If this renders the knee stable, fusion of the ankle in the proper degree of equinus will do likewise.

The amount of equinus was measured on the lateral roentgenogram by the intersection of a line drawn parallel to the long axis of the tibia and another line drawn from the plantar surface of the first metatarsal head to the plantar surface of the os calcis. Ten ankles were fused at 92 to 95 degrees of dorsiflexion, 29 at 95 to 100 degrees, 22 at 100 to 105 degrees, 10 at 105 to 110 degrees and 1 at 112 degrees.

In 62 of the 72 cases the end results were considered good. In 1 the ankle was fused in too much equinus (112 degrees of dorsiflexion), and in another, in not enough equinus (92 degrees of dorsiflexion). In 2 cases there was need of a subtalar triple arthrodesis because of "fore foot drop" and lateral instability. In 2 cases a revision of the existing subtalar triple arthrodesis was needed. Four patients were relieved of the drop foot deformity but continued to have an unstable knee.

CALCANEUS DEFORMITY

There were 34 cases of ankle fusion to correct calcaneus deformity. Twenty-two of the patients were males and 12 were females. Their ages at operation ranged from 8 to 44 years, the majority being in the second or third decade. In 31 patients of this group a subtalar triple arthrodesis had been previously done because of lateral instability or cavus deformity of the foot. The involved extremities presented from ½ to 3¼ inches (1.2 to 8.2 cm.) of actual shortening; in 1 instance the leg was ⅝ inch (1.9 cm.) longer than its fellow.

Nine patients with a paralytic calcaneus deformity also had an unstable knee. In 8 of these the knee was stabilized by ankle fusion. In 7 instances the ankles were fused at 90 to 95 degrees of dorsiflexion, in 17 at 95 to 100 degrees and in 10 at 100 to 105 degrees.

Of these 34 cases, the end results in 23 were considered good. In 8 the ankles were fused in not enough equinus (90, 90, 92, 94, 95, 98, 99 and 99 degrees of dorsiflexion). In 2 cases a subtalar triple arthrodesis was needed because of cavovalgus deformity of the foot. One patient was relieved of the calcaneus deformity but continued to have an unstable knee.

OPERATIVE PROCEDURE AND POSTOPERATIVE CARE

The anterior approach is used for arthrodesis of the ankle. An intra-articular fusion is done, tibial bone chips being used to promote osteogenesis. Care is taken to avoid exposure of or injury to the lower

Fig. 3.—Preoperative lateral view of a drop foot deformity (with associated instability of the knee) due to anterior poliomyelitis.

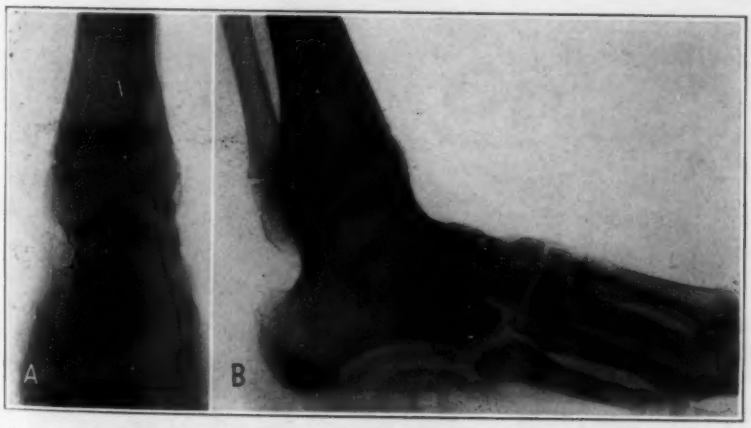

Fig. 4.—*A*, anteroposterior view and *B*, lateral view of the ankle shown in figure 3, nineteen months after ankle fusion (preceded by subtalar triple arthrodesis.) The ankle was solidly fused at 102 degrees of dorsiflexion. The knee was stable. The lower tibial and fibular epiphysial lines were still open.

tibial epiphysial cartilage. The technic of the operative procedure has been recently described by Liebolt.[2]

A long leg plaster cast is applied with the foot in the estimated proper degree of equinus. Care must be taken to see that the front part of the foot is in the maximum degree of dorsiflexion on the rear part, as this is its weight-bearing position. Postoperative roentgenograms will determine the degree of equinus. If it is too great or too little it can be corrected by wedging the cast. Theoretically, it is better to err in the direction of too much equinus, since wedging into more dorsiflexion will serve to occlude the joint space further. (Of the 106 cases, postoperative wedging was done in 27. All 27 ankles went on to solid bony union in the usual time, and in no case did delayed union result from the postoperative wedging.) At the end of six weeks, weight bearing in a short walking cast is allowed. At the end of another six weeks the cast is removed and the solidity of the fusion is checked with roentgenograms. The shoe can then be adjusted if necessary. Lifts in the heel or in the heel and sole can compensate for any shortening of the extremity and for the equinus of the foot. If the ankle has been fused in too little equinus and there is associated instability of the knee, a metatarsal bar on the sole of the shoe is of benefit.

Of the 106 cases in which operation was done, solid arthrodesis was obtained in 102. In 92 the ankles were solidly fused at the end of twelve weeks, in 10, additional periods of one to eight weeks were required before solid bony ankylosis resulted. Four ankles (3 drop-foot deformities and 1 calcaneus deformity) failed to fuse solidly, an incidence of 4 per cent of pseudarthroses. All four subsequently were solidly arthrodesed by a second operation. Only one ankle fusion was revised. The ankle was solidly fused but was reoperated on in order to obtain more equinus, which was needed to stabilize the knee.

PROPER DEGREE OF EQUINUS

The success of the procedure depends largely on arthrodesing the ankle in the proper degree of equinus. Factors to be taken into consideration are:

1. Sex of the patient. Women's high-heeled shoes require more equinus than do men's low-heeled ones.
2. Degree of shortening of the involved extremity, if any.
3. Presence or absence of associated instability of the knee.

An excellent way to determine before operation the degree of equinus desired is to take a lateral roentgenogram with the patient standing while wearing a shoe with the heel height of his or her choice. This

2. Liebolt, F. L.: Pantalar Arthrodesis in Poliomyelitis, Surgery **6**:31 (July) 1939.

Fig. 5.—Preoperative lateral view of a foot and ankle with a calcaneus deformity (with associated instability of the knee) due to anterior poliomyelitis. A subtalar triple arthrodesis had been performed previously.

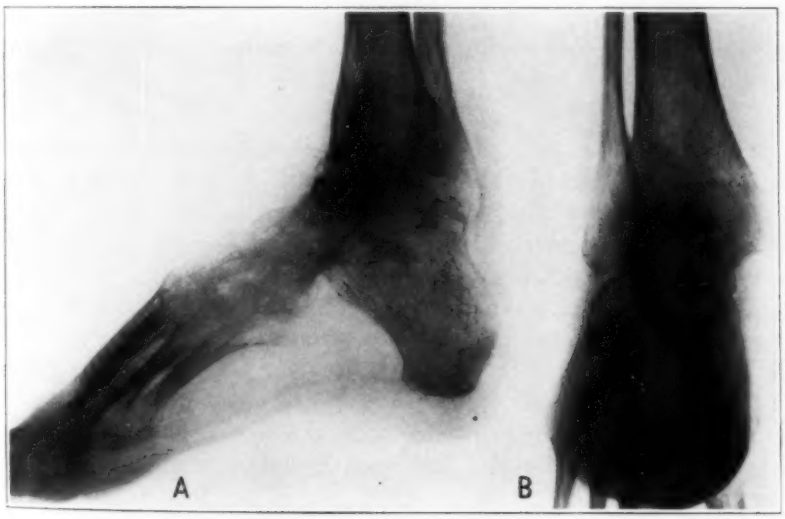

Fig. 6.—*A*, lateral view and *B*, anteroposterior view of the ankle shown in figure 5, twelve weeks after ankle fusion. The ankle was solidly fused at 98 degrees of dorsiflexion. The knee was stable.

applies to simple drop foot or calcaneus deformity. The plaster equinus boot test is more accurate when there is an unstable knee; the lateral roentgenogram of the foot and ankle in the equinus boot gives the desired degree of equinus.

In general, it is felt that the best functional position is 5 to 10 degrees of equinus for men and 10 to 15 degrees for women.

COMMENT

Ankle fusion for the correction of drop foot or calcaneus deformity is mechanically sound and is relatively simple technically. In this series of 106 cases there was no disturbance of growth, nor should there be any such disturbance with proper operative care.[3] Arthrodesis of the ankle joint does not impair normal function of the extremity. If the ankle has been fused in the proper degree of equinus, it is often difficult or impossible to say which ankle has been arthrodesed by simply watching a patient walk and observing his gait. Any noticeable limp is usually due to concurrent muscular imbalance or to inequality in the length of the legs. It is true that after ankle fusion a patient's gait is usually poorer without shoes than with shoes on. However, the excellence of his gait with his shoes on more than offsets this disadvantage.

If a subtalar triple arthrodesis is to also be done, it should be done first; then, with the subsequent ankle fusion, the foot can be more accurately alined with the leg to obtain the optimum degree of desired equinus.

SUMMARY

One hundred and six ankle fusions were done in a five year period (1934 to 1938 inclusive) on patients with residual anterior poliomyelitis at the New York Orthopaedic Dispensary and Hospital. Of these, 72 were done for paralytic drop foot and 34 for paralytic calcaneus deformities. The patients have been carefully followed, the follow-up period ranging from seven months to five and one-half years. In 85 cases (80 per cent) the end result was good. In 10 (9 per cent) the end result was only fair, there being either too much or too little equinus. In 5 (5 per cent) the end result was good so far as the ankle was concerned but an associated unstable knee was not rendered stable. In 6 (per cent) the end result was good so far as the ankle was concerned but an associated lateral instability of the foot needed further operative stabilization of the subtalar and midtarsal joints. In no case were the results considered poor. Of 32 unstable knees, 27 (84 per cent) were stabilized by ankle fusion. There was no resulting inter-

3. Turner, H.: Deformities of Foot Associated with Arthrodesis of Ankle Joint Performed in Early Childhood, J. Bone & Joint Surg. **16**:423 (April) 1934.

ference with growth in any case. Functional use of the involved extremity was improved in all cases. In 4 cases (4 per cent) pseudarthrosis developed, but in all 4 the joint became solidly arthrodesed after refusion.

CONCLUSION

Ankle fusion is a satisfactory method of treating drop foot and calcaneus deformities regardless of the cause. It results in freedom from disability caused by deformity, pain or instability. In a fused ankle there is no pain, bony impingement or swelling such as occurs at times after bone block operations. The operative procedure is relatively simple in contrast to such methods as the Lambrinudi operation [4] and its modifications. An additional advantage is that associated instability of the knee can often be corrected by ankle fusion. The end results are uniformly satisfactory as indicated by this five year study of 106 cases.

It is important to avoid injury to the epiphysial cartilages of the distal ends of the tibia and fibula if they are still present. The end result is determined by the degree of equinus obtained. Five degrees to 10 degrees of equinus for males, and 10 to 15 degrees of equinus for females is in general satisfactory.

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4. Lambrinudi, C.: New Operation on Drop-Foot, Brit. J. Surg. **15**:193 (Oct.) 1927.

EXPERIMENTAL GOITER DUE TO CALCIUM

C. ALEXANDER HELLWIG, M.D.
WICHITA, KAN.

Until recently, endemic goiter was regarded as a deficiency disease due to lack of iodine in food and drinking water. Newer studies have called attention to the importance of positive goitrogenic factors.

The observation of Webster, Clawson and Chesney [1] that feeding cabbage to rabbits causes goiter in a short time proved that a dietary factor much more powerful than any iodine deficiency may be responsible for goiter.

During the last few years, another positive goitrogenic agent has been demonstrated. Using lime, calcium chloride or calcium carbonate in conjunction with a diet low in iodine, Tanabe,[2] Hellwig,[3] Thompson [4] and Hibbard [5] produced goiters in white rats.

In experiments during 1929 and 1932 I was unable to obtain hyperplasia of the thyroid in white rats by lack of iodine alone. I concluded that iodine deficiency by itself cannot be the essential cause of endemic goiter and that there must be, rather, a positive goitrogenic agent. My standpoint was supported by Hibbard's [5] experiments in a nonendemic region. In a recent paper, Kenyon [6] objected to my conclusions and pointed out that Remington and Levine,[7] Krauss and Monroe [8] and

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From the Department of Pathology, St. Francis Hospital.

1. Webster, B.; Clawson, T. A., and Chesney, A. M.: Endemic Goiter in Rabbits, Bull. Johns Hopkins Hosp. **43**:278, 1928.

2. Tanabe, H.: Experimenteller Beitrag zur Aetiologie des Kropfes, Beitr. z. path. Anat. u. z. allg. Path. **73**:415, 1925.

3. Hellwig, C. A.: Iodine Deficiency and Goiter: Influence of Diet Poor in Iodine on Thyroid Gland in White Rats, Arch. Path. **11**:709 (May) 1931; Experimental Goiter: Functional, Chemical and Histological Studies, ibid. **19**:364 (March) 1935.

4. Thompson, J.: Influence of the Intake of Calcium on the Thyroid Gland of the Albino Rat, Arch. Path. **16**:211 (Aug.) 1933.

5. Hibbard, J. S.: Experimental Thyroid Hyperplasia: Increased Intake of Chloride Combined with Diet Deficient in Iodine as Factor, Arch. Surg. **26**:648 (April) 1933.

6. Kenyon, A. T.: Histological Changes in Thyroid Gland of White Rat Exposed to Cold, Am. J. Path. **9**:347, 1933.

7. Remington, R. E., and Levine, H.: Studies on the Relation of Diet to Goiter, J. Nutrition **11**:343, 1936.

8. Krauss, W. E., and Monroe, C. F.: Comparison of Influence of Iodized Milk and of Potassium Iodide Administered Directly on Size and Iodine Content of Thyroid Gland of Rats, J. Biol. Chem. **89**:581, 1930.

Hayden, Wenner and Rucker [9] have reported hyperplasia of the thyroid occurring in white rats on a diet deficient in iodine. An analysis of the goitrogenic diets used by these authors reveals, however, that they contained, without exception, an abundance of calcium.

Since my first successful attempts to produce goiter in white rats with calcium, the studies of Hibbard,[5] Thompson [4] and Stiner [10] have brought up new questions. Hibbard [5] produced hyperplasia of the thyroid by giving calcium chloride, while calcium lactate was without effect. He therefore expressed the opinion that the chlorine ion rather than the calcium ion is responsible for the development of goiter. Thompson [4] found that the thyroids of rats fed a goitrogenic diet for longer than three months underwent secondary atrophy. At the first International Goiter Conference, Stiner [10] stated that lack of vitamins is an important factor in the etiology of goiter.

It seemed advisable to repeat my experimental studies under conditions which would take into consideration the three questions which arose from the work of Hibbard,[5] Thompson [4] and Stiner: [10] 1. Is calcium carbonate as effective in producing hyperplasia of the thyroid as calcium chloride? 2. Does a prolonged experimental feeding reduce the size of the thyroid? 3. Does addition of vitamins to the goitrogenic diet prevent goiter?

EXPERIMENTAL DATA

The recent experiments were begun on Sept. 12, 1938, with 40 male white rats. All the animals were of the same age, 16 weeks, and approximately of the same weight. They were housed in lots of 10 in Dormer cages which had floors of mesh wire. In order to maintain the utmost cleanliness no hay or other material was used for bedding. The cages were kept in a well lighted room at a constant temperature of 20 C. to prevent any effect on the thyroid of darkness or low temperature. The experimental diet for each animal consisted of yellow corn meal (7 Gm.), rolled oats (2 Gm.), calcium carbonate (0.3 Gm.), sodium chloride (0.1 Gm.) and tomato juice (1 cc.). Ten animals (series 1) received this diet with pure drinking water. Thirty animals (series 2) were given the same food, but as drinking water they were given a 2 to 10,000,000 solution of potassium iodide. This corresponded to a daily intake of 2 micrograms of potassium iodide for each animal. Groups of experimental animals were killed with chloroform three, five and eight months after the beginning of the feeding.

The thyroids were dissected immediately after death, measured and at once preserved in a 10 per cent concentration of solution of formaldehyde U. S. P. After embedding in paraffin, the cervical organs were cut in horizontal plane, and the sections that included the isthmus and both lobes of the thyroid were selected for microscopic study.

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9. Hayden, E. M.; Wenner, W. T., and Rucker, C. W.: Production of Goiter in Rats by Restricted Iodine Feeding, Proc. Soc. Exper. Biol. & Med. **21**:546, 1924.

10. Stiner, O.: Zur Verbreitung des endemischen Kropfes in der Schweiz, in Compte rendu Conference Internationale du Goitre, Berne, Hans Huber, 1928, p. 403.

RESULTS

From tables 1 and 2 it is evident that the diet rich in calcium produced a definite enlargement of the thyroid. No decrease in size of the gland was noticed in animals fed such a diet for five and eight months. The animals of the first series showed large goiters with marked

TABLE 1 *(Series 1).—Results Obtained with Male White Rats Fed Yellow Corn Meal, Rolled Oats, Calcium Carbonate, Tomato Juice and Pure Water*

Rat	Weight, Gm.	Duration of Experiment, Months	Size of Thyroid, Mm.	
			Right Lobe	Left Lobe
1	230	3	8 by 3 by 2	7 by 4 by 2
2	225	3	7 by 2 by 3	7 by 3 by 4
3	130	3	7 by 3 by 3	7 by 2 by 3
4	140	5	7 by 4 by 2	6 by 3 by 2
5	116	5	7 by 3 by 2	6 by 3 by 2
6	145	5	6 by 4 by 2	7 by 4 by 2
7	115	5	5 by 4 by 2	6 by 4 by 2
8	222	5	7 by 4 by 3	7 by 4 by 3

TABLE 2 *(Series 2).—Results Obtained with Male White Rats Fed Same Calcium-Rich Diet Supplemented with 2 Micrograms of Potassium Iodide Daily*

Rat	Weight, Gm.	Duration of Experiment, Months	Size of Thyroid, Mm.	
			Right Lobe	Left Lobe
1	260	3	6 by 3 by 2	6 by 2.5 by 2
2	250	3	6 by 3 by 2	6 by 3 by 2
3	160	3	7 by 3 by 2	6 by 3 by 2
4	230	5	8 by 3 by 2	7 by 4 by 2
5	255	5	6 by 4 by 2	7 by 4 by 2
6	118	5	6 by 2 by 1.5	6 by 3 by 2
7	220	5	8 by 4 by 2	9 by 4 by 2
8	145	5	6 by 3 by 1.5	6 by 4 by 2
9	155	5	8 by 3 by 2	7 by 3 by 2
10	156	8	5 by 3 by 1	7 by 3 by 2
11	140	8	6 by 3 by 2	6 by 2 by 1
12	130	8	6 by 2 by 3	6 by 2 by 2
13	156	8	6 by 3 by 2	6 by 3 by 2
14	150	8	6 by 3.2 by 2	6.1 by 3.2 by 2
15	140	8	6 by 3 by 2	5 by 3 by 2
16	240	8	7 by 4 by 3	6 by 3 by 2
17	144	8	7 by 4 by 2	6 by 2.5 by 2
18	138	8	5 by 3 by 2	7 by 3 by 2
19	244	8	8 by 4 by 3	6 by 3 by 2

hyperemia. The size of the centrally located acini was between 30 and 40 microns. The lumens appeared empty or contained scanty, lightly stained colloid. The acinar epithelium was from 8 to 10 microns high. The blood vessels were filled with blood cells. The glands resembled grossly and microscopically those observed in my former experiments with calcium chloride. The 30 animals of the second series, which had received the same calcium-rich diet but in addition had been given ten times the physiologic requirement of iodine, had slightly smaller thyroids than had the first group. The enlarged glands were light

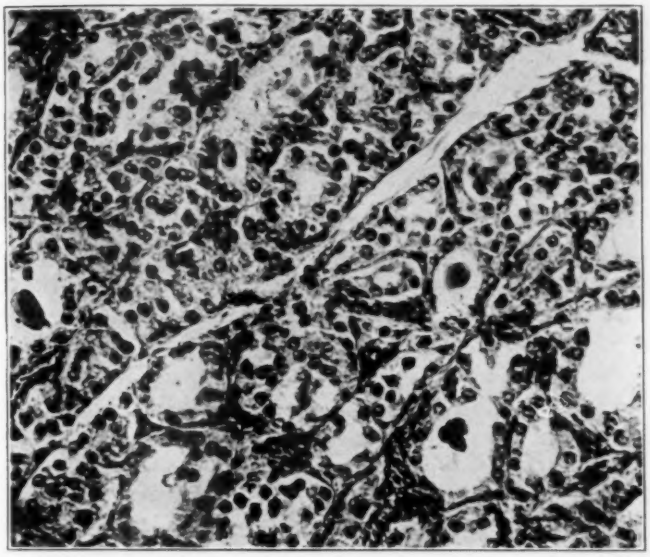

Fig. 1.—Diffuse parenchymatous goiter produced in a white rat by a diet high in calcium and low in iodine.

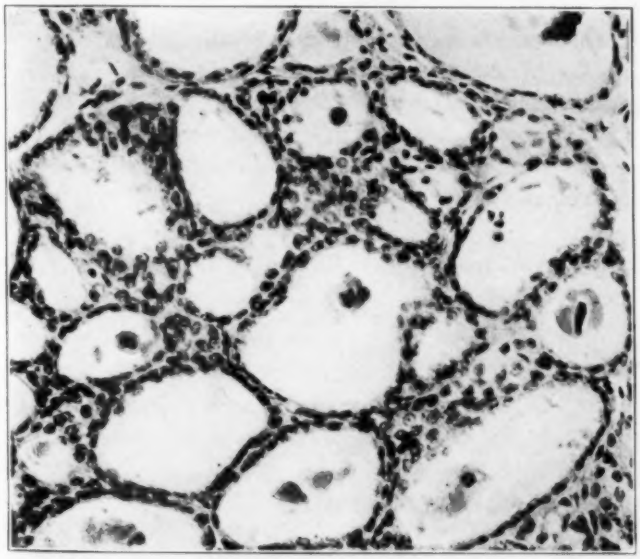

Fig. 2.—Diffuse colloid goiter produced in a white rat by a diet high in calcium and ten times the normal requirement of iodine.

brown. The diameter of the central acini varied between 80 and 120 microns. Many wide acini were observed throughout the gland. Solid or tubular acini were almost completely absent. The colloid was well stained with eosin. The height of the acinar epithelium was between 4 and 6 microns. Sections of these thyroids showed colloid goiter with mild epithelial proliferation.

COMMENT

The recent experiments have thus shown that goiter can be produced with regularity in white rats by a diet consisting of corn meal, rolled oats and calcium carbonate. The goitrogenic factor in this diet is the calcium ion. Secondary atrophy of the thyroid was not observed in spite of the fact that the experimental period was extended to eight months. The addition of vitamins in the form of tomato juice did not interfere with the goitrogenic action of the calcium.

The structure of the experimental goiters varied according to the iodine content of the goitrogenic diet. A diet rich in calcium and low in iodine produced parenchymatous goiter; a diet rich in calcium and relatively rich in iodine produced colloid goiter. The results of my experiments explain the fact that in regions where the iodine content of the food is sufficient for a normal intake, goiter will develop if a powerful positive goitrogenic factor is present. Under these conditions, which are found in level regions (North America; northern Europe), the resulting goiter will be a colloid goiter. The theory of iodine deficiency will never explain the development of colloid goiter.[11]

The results of these experiments are not only of theoretic interest but of great practical value from the standpoint of prophylaxis. The daily intake of iodine required to prevent goiter is apparently not a constant. It varies, depending on the presence and intensity of the positive goitrogenic factor.

CONCLUSIONS

1. Calcium carbonate is as effective in producing goiter in white rats as is calcium chloride.

2. Addition of vitamins to the goitrogenic diet does not prevent hyperplasia of the thyroid.

3. Prolonged feeding of the goitrogenic diet does not produce secondary atrophy of the thyroid.

4. Addition of ten times the normal requirement of iodine to the goitrogenic diet produces colloid goiter.

5. Positive goitrogenic factors must be considered in the etiology of goiter.

6. The amount of iodine required to prevent goiter is variable and depends on the presence and intensity of positive goitrogenic agents.

11. Hellwig, C. A.: The Diffuse Colloid Goiter, West. J. Surg. **47**:406, 1939.

ETIOLOGY OF STONE IN THE COMMON BILE DUCT

R. FRANKLIN CARTER, M.D.

CARL H. GREENE, M.D., PH.D.

J. RUSSELL TWISS, M.D.

AND

RICHARD HOTZ, M.D.

NEW YORK

An increasing interest in functional disturbances which may be the underlying cause of pathologic changes in the common bile duct is manifest in the recent literature. Improvement of the technic of cholangiography for the study of dysfunction and pathologic conditions of the common duct has been the means of increasing knowledge of functional disturbances that seem to terminate in organic disease. This knowledge, as well as that derived from careful follow-up studies of cholecystectomized patients, has led to more frequent exploration of the common duct in recent years and, therefore, to an apparent increase in the incidence of stone in the common duct (Clute,[1] Lahey,[2] Cheever,[3] Cattell [4] and others).

Kehr,[5] Deaver,[6] Moynihan,[7] Lahey,[8] Hermanson and Goldowsky [9] and Maingot [10] are among the many authors who have emphasized the

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From the Clinic for the Study of Disease of the Biliary Tract, New York Post-Graduate Medical School and Hospital.

1. Clute, H. M.: Common Duct Stones, J. A. M. A. **95**:1568 (Nov. 22) 1930.

2. Lahey, F. H.: Common and Hepatic Duct Stones, New England J. Med. **207**:685, 1932. Lahey, F. H., and Swinton, N. W.: Stones in the Common and Hepatic Bile Ducts, ibid. **213**:1275, 1935. Lahey, F. H.: Earlier Operations in Cholelithiasis, S. Clin. North America **17**:725, 1937.

3. Cheever, D.: Methods and Results in the Surgical Treatment of Diseases of the Biliary Passages, New England J. Med. **213**:463, 1935.

4. Cattell, R. B.: The Technique of Cholecystectomy and Choledochostomy, S. Clin. North America **17**:731, 1937.

5. Kehr, H.: Wann soll man nach einer Ektomie bei negativem Palpationsbefund von Steinen im Choledochus diesen Gang incidieren und drainieren und wann nicht? Arch. f. klin. Chir. **97**:301, 1912.

6. Deaver, J. B.: Surgery of the Common Bile Duct, M. Rec. **80**:909, 1911.

(Footnotes continued on next page)

frequent neglect or oversight of lesions of the common bile duct, especially calculi. Young [11] observed that stones were still present at autopsy in the common bile ducts of 61 per cent of 67 patients who died of complications following cholecystectomy. Heyd and one of us (R. H.) [12] have shown in a previous publication that the incidence and severity of pathologic change in the common bile duct are directly proportional to the duration and severity of the preexisting disease of the gallbladder.

That this trend toward earlier surgical intervention in disease of the gallbladder has not prevented the secondary formation of calculi of the common duct has particularly stimulated the study of those factors which may be the cause of the formation of such stones in an attempt to prevent their occurrence.

It is our purpose to review briefly the literature on the normal and abnormal function of the common bile duct and to present our clinical pathologic studies of patients with disease of the common duct.

NORMAL PHYSIOLOGY OF THE COMMON DUCT

The function of the common duct is that of a conduit between the hepatic and cystic ducts and the duodenum. Its major structure is the sphincter of Oddi, found by Westphal [13] to consist of a proximal muscular sleeve and a distal group of muscle fibers surrounding the ampulla of Vater. Normally the opening is only 1 to 2 mm. in diameter.[14] This mechanism controls the flow of the bile into the duodenum, normally an intermittent function dependent on a number of stimuli (Rost; [15]

7. Moynihan, B.: Secondary Operations on the Biliary System, Lancet **2**:4, 1923.

8. Lahey, F. H.: The Incidence and Management of Stones in the Common and Hepatic Ducts, Tr. Am. S. A. **51**:164, 1933.

9. Hermanson, L., and Goldowsky, S.: Occurrence of Common Duct Stone Following Gallbladder Operations, New England J. Med. **211**:806, 1934.

10. Maingot, R.: Biliary Tract Surgery, Post-Grad. M. J. **13**:213, 1937.

11. Young, E. L.: Possibilities of Failure in Removal of Stones in Biliary Tract, New England J. Med. **200**:1145, 1929.

12. Heyd, C. G., and Hotz, R.: Surgery of the Common Duct, Am. J. Surg. **44**:677, 1939.

13. Westphal, K.: Die Bewegungs- und Resorptionsstörungen an den Gallenwegen und ihre Gefahren, Verhandl. d. deutsch. Gesellsch. f. inn. Med., 1932, Kong. 44, p. 354.

14. Weiss, S.: Diseases of the Liver, Gallbladder, Ducts and Pancreas, New York, Paul B. Hoeber, Inc., 1935.

15. Rost, F.: Die funktionelle Bedeutung der Gallenblase: Experimentelle und anatomische Untersuchungen nach Cholecystektomie, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **26**:710, 1913.

Mann;[16] Mann and Bollman,[17] and others). Rost observed that after extirpation of the gallbladder in dogs a continuous trickle of bile flowed from the ampulla and so contributed experimental evidence of a reciprocal contrary innervation between the gallbladder and the sphincter of Oddi. Such an innervation hypothecates that during the resting phase of activity of the gallbladder the organ is relaxed and allowed to fill by the tonicity of the sphincter of Oddi, whereas certain stimuli, notably food and hydrochloric acid in the duodenum, cause the sphincter to relax and the gallbladder to contract. Mentzer,[18] Berg,[19] Berg and Jobling,[20] McMaster and Elman,[21] Whitaker,[22] Ravdin and Johnston[23] and Boyden[24] have expressed a contrary opinion. Bollman and Mann concluded that the normal intermittent flow of bile from the ampulla of the dog is due to the action of the duodenal musculature. The entire problem of dyskinesia of the gallbladder, as presented by Ivy and Sandbloom,[25] and that of dyskinesia of the common duct, as elaborated by Best and Hicken,[26] is dependent on a disturbance of the probable reciprocal relation just described.

Contraction or spasm of the common duct elsewhere than at its terminal portion (sphincter of Oddi) is highly questionable in view of

16. Mann, F. C.: A Study of the Tonicity of the Sphincter at the Duodenal End of the Common Duct, J. Lab. & Clin. Med. **2**:107, 1919; The Function of the Gallbladder, Physiol. Rev. **4**:251, 1924.

17. Mann, F. C., and Bollman, J. L.: Jaundice: A Review of Some Experimental Investigations, J. A. M. A. **104**:371 (Feb. 2) 1935.

18. Mentzer, S. J.: The Disturbances of the Law of Contrary Innervation as a Pathologic Factor in Diseases of the Bile Ducts and the Gallbladder, Am. J. M. Sc. **153**:469, 1917.

19. Berg, B. N.: Gallbladder Function After Division of the Common Duct, Surg., Gynec. & Obst. **46**:464, 1927.

20. Berg, B. N., and Jobling, J. W.: The Effect of Division and Transplantation of the Common Duct upon the Gallbladder, Proc. Soc. Exper. Biol. & Med. **24**:434, 1927.

21. McMaster, P. D., and Elman, R.: On the Expulsion of Bile by the Gallbladder and a Reciprocal Relationship with the Sphincteric Activity, J. Exper. Med. **44**:173, 1926.

22. Whitaker, L. R.: The Mechanism of the Gallbladder and Its Relationship to Cholelithiasis, J. A. M. A. **88**:1542 (May 14) 1927.

23. Ravdin, I. S., and Johnston, C. G.: The Gallbladder: Recent Advances as Applied to Treatment, Pennsylvania M. J. **35**:357, 1932.

24. Boyden, E. A.: Sphincter of Oddi in Man and Certain Representative Mammals, Surgery **1**:25, 1937.

25. Ivy, A. C., and Sandbloom, P.: Biliary Dyskinesia, Ann. Int. Med. **8**:115, 1934.

26. Best, R. R., and Hicken, N. F.: Biliary Dyssynergia, Surg., Gynec. & Obst. **61**:721, 1935.

the careful anatomic study made by MacDonald.[27] He could demonstrate no circular muscle fibers and only occasional isolated longitudinal fibers in the wall of the common bile duct in man. Mirizzi,[28] however, claimed to have seen typical spastic defects in the common hepatic ducts of patients for whom cholangiographic study was made. He noted the disappearance of such defects in subsequent roentgenograms. Such defects have been attributed by other observers to the presence of mucus in the duct.

The mucous membrane of the common duct is irregular and broken by minute depressions which open or lead to two types of structures, small saclike appendages called parietal sacculi (Theile[29]) and short blind ducts called vasa aberrantia (Holmes[30]). Their function is not known, although Beale[31] concluded that they are accessory gallbladders capable of taking over the function of the gallbladder when it is diseased; Ravdin and Johnston attributed a glandular activity to these structures. The mucous membrane of the common duct or its appendages does secrete a watery alkaline solution into the lumen of the common duct (Rous and McMaster[32]), though the role and the volume of this diluting solution have not been determined.

PATHOLOGIC PHYSIOLOGY OF THE COMMON BILE DUCT

Studies on the common duct of animals, particularly dogs, and cholangiographic study of the common duct of the human being, as practiced by Mirizzi,[33] Saralegui,[34] Walters and Theeson,[35] Best and

27. MacDonald, I. S.: Histology of the Biliary Ducts and Its Correlation with the Symptomatology of Common Duct Stone, Surg., Gynec. & Obst. **60**:775, 1935.

28. Mirizzi, P. L.: Operative Cholangiography: Contribution to Physiopathology of the Common Bile Duct, Lancet **2**:366, 1938.

29. Theile, I.: Die Leber, in Wagner, R.: Handwörterbuch der Physiologie, Brunswick, F. Vieweg u. Sohn, 1842-1853, vol. 2, p. 349.

30. Holmes, B.: The Mucous Glands of the Bile Ducts and Gallbladder, Lancet **1**:678, 1911.

31. Beale, L. S.: Lectures on the Principles and Practice of Medicine: The Liver, London, J. & A. Churchill, 1899.

32. Rous, P., and McMaster, P. D.: Physiological Factors in Genesis of Gall Stones, Proc. Inst. Med. Chicago **7**:33, 1928.

33. Mirizzi, P. L.: La colangiografía durante las operaciones de las vias biliares, Bol. y trab. de la Soc. de cir. de Buenos Aires **16**:1133, 1932; La cholangiographie durant l'opération (C. D. O.): Constatations et résultats de la seconde série de cent opérations seniles voies biliares, Bull. et mém. Soc. nat. de chir. **61**:349, 1935; Die Anwendung der Cysticoduodenostomie, Deutsche Ztschr. f. Chir. **246**:609, 1936; Operative Cholangiography, Surg., Gynec. & Obst. **65**:702, 1937.

34. Saralegui, J. A.: Cholangiography: New Technique and Results, Am. J. Roentgenol. **32**:167, 1934; Die Cholangiographien beim Studien der Gallenleiden, Fortschr. a. d. Geb. d. Röntgenstrahlen **52**:571, 1935.

(Footnotes continued on next page)

Hicken [36] and others, form the basis of such knowledge as physicians now possess of the abnormal function of the extrahepatic bile ducts. From such studies certain assumptions have been made possible, especially as to function of the common bile duct after cholecystectomy.

It is generally recognized that the common bile duct in man assumes some of the function originally resident in the gallbladder when the latter is extirpated by operation or by disease. Sweet,[37] in 1924, found the parietal sacculi of the hepatic ducts and of the common bile duct enlarged after cholecystectomy. From his chemical studies of the blood of cholecystectomized dogs he made the deduction that the parietal saccules assume the function of the gallbladder, particularly in regard to absorption of cholesterol. Boyd [38] stated a similar opinion. An enlargement of the vasa aberrantia has also been described by Boyd,[38] Sweet,[37] Sutton [39] and Schmidt and Ivy.[40] Counseller [41] did not find these changes except when the common duct itself is dilated. This dilatation is common after partial intermittent obstruction and after cholecystectomy, as has been pointed out by Judd and Mann.[42] Cox,[43] in a study of autopsy specimens from cholecystectomized patients, concluded that the dilatation of the accessory structures is merely concomitant with dilatation of the common duct and is not a specific response to cholecystectomy. He was able to demonstrate no epithelial hypertrophy or secretory glands before or after obstruction of the common duct or cholecystectomy and therefore concluded that the appendages have no specific function. That the

35. Walters, W., and Theeson, N. W.: Visual Methods of Studying the Physiology of the Common Bile Duct: I. The Problem of Pancreatitis and Sphincteritis, Proc. Staff Meet., Mayo Clin. **9**:772, 1934.

36. Best, R. R., and Hicken, N. F.: Cholangiographic Demonstration of Biliary Dyssynergia and Other Obstructive Lesions of the Gallbladder and Bile Ducts, J. A. M. A. **107**:1615 (Nov. 14) 1936; Biliary Dyssynergia: Cholangiographic Recognition and Its Significance, West. J. Surg. **44**:467, 1936; Technique of Immediate Cholangiography, Surg., Gynec. & Obst. **65**:217, 1937.

37. Sweet, J. E.: The Gallbladder: Its Past, Present, and Future, Internat. Clin. **1**:187, 1924.

38. Boyd, W.: Studies in Gallbladder Pathology, Brit. J. Surg. **10**:337, 1923.

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41. Counseller, V. S.: Certain Effects of Obstruction of the Bile Ducts, Ann. Surg. **87**:210, 1928.

42. Judd, E. S., and Mann, F. C.: The Effect of the Removal of the Gallbladder: An Experimental Study, Surg., Gynec. & Obst. **24**:437, 1917. Mann, F. C.: A Physiologic Consideration of the Gallbladder, J. A. M. A. **83**:829 (Sept. 13) 1924.

43. Cox, F. M.: Changes in the Bile Ducts and Parietal Saccules Following Absence of the Gallbladder, Surg., Gynec. & Obst. **55**:169, 1932.

dilatation observed after cholecystectomy is dependent on the function of the sphincter of Oddi has been demonstrated by Judd and Mann,[42] Doubilet and Colp [44] and Winkelstein and Aschner.[45] They were unable to secure dilatation of the common duct if the sphincter had been destroyed or the ampulla cannulized.

In 1903, Krukenberg reported a case of gallbladder colic without gallstones. Since that time, not only colic but dilatation of the gallbladder and the common duct without stones or evident obstruction has been increasingly recognized and attributed to a neurogenic mechanism which increases the tone of the sphincter of Oddi (Best and Hicken; [36] Ivy and Sandbloom; [25] Berg; [19] Walters, McGowan, Butsch and Knepper,[46] and others). Ivy,[47] Potter and Mann [48] and Doubilet and Colp [44] have found pressures up to 400 mm. of water necessary to overcome the resistance of spastic sphincters. Best and Hicken [36] and others have shown such an increased tone to be the cause for dilatation of the common duct, a view contrary to the results of experimental studies of Puestow.[49] They concluded that such a spastic dysfunction causes stagnation of bile and is the precursor of infection and calculi, a view also held in part by Beer,[50] Walters [51] and Beall [52] for intrahepatic stones.

The recurrent stones found in some common ducts after cholecystectomy and prolonged drainage of the common duct when no organic obstruction is demonstrable can probably best be explained on the basis of continuing spasm and infection. Puestow,[49] in a study of 85 cholecystectomized patients, found a total lack of tone in the sphincter in the majority of instances and concluded that the dilatation of the common duct is passive or atonic. This contention is difficult to appraise, in view

44. Doubilet, H., and Colp, R.: Resistance of the Sphincter of Oddi in the Human, Surg., Gynec. & Obst. **64**:622, 1937; Endocholedochal Sphincterotomy, ibid. **66**:882, 1938.

45. Winkelstein, H., and Aschner, P. W.: The Mechanism of the Flow of Bile from the Liver into the Intestines, Am. J. M. Sc. **171**:104, 1926.

46. Walters, W.; McGowan, J. M.; Butsch, W. L., and Knepper, P. A.: Pathologic Physiology of the Common Bile Duct: Its Relation to Biliary Colic, J. A. M. A. **109**:1591 (Nov. 13) 1937.

47. Ivy, A. C.: Physiology of the Gallbladder, Physiol. Rev. **14**:1, 1934.

48. Potter, J. C., and Mann, F. C.: Pressure Changes in the Biliary Tract, Am. J. M. Sc. **171**:202, 1926.

49. Puestow, C. B.: Changes in Intracholedochal Pressure Following Cholecystectomy, Surg., Gynec. & Obst. **67**:82, 1938.

50. Beer, E.: Intrahepatic Cholelithiasis, M. News **85**:202, 1904.

51. Walters, W.: The Pathologic Physiology of Stone in the Common Bile Duct, Surg., Gynec. & Obst. **63**:417, 1936.

52. Beall, F. C.: Stones in the Common Bile Duct, Ann. Surg. **107**:238, 1938.

of the clinical and experimental data which contradict it. Newman [53] has noted temporary atony of the sphincter following cholecystectomy, but the tone rapidly returned to normal or increased levels, a cycle we have noted cholangiographically in our own studies.

It is probable that the course of events in the formation of recurrent calculi of the common duct without organic obstruction is that of increased spasm of the sphincter causing laking or stagnation of bile with oversaturation and therefore precipitation of cholesterol and calcium salts. Continued stagnation and precipitation tend toward the formation of stones, which, as in the gallbladder, predispose to irritation of the mucous membrane and infection. Whether infection of the common duct precedes or follows the formation of stone is debatable and of little consequence in this discussion. That the two are frequently coexistent has been demonstrated by many observers cited previously in this section.

RESULTS OF STUDY ON DISEASE OF THE COMMON DUCT

During the past seven years, 239 operations were performed on the gallbladders and bile ducts of patients who had been studied in the "gallbladder clinic" of the New York Post-Graduate Medical School and Hospital. In 47 instances, or 20 per cent, exploration of the common duct was performed. As in other clinics, the frequency of exploration of the common duct in this institution has increased during the past few years; in 30 per cent of the last 100 cases of this series such an exploration was done. Stones were present in 21 cases; in all of the remainder there was dilatation of the common bile duct due either to spasm of the sphincter or to some obstruction other than stone. A comparison between these two groups of cases, i. e., those in which stones were present and those in which they were absent, has been undertaken with the hope of determining the etiology of the common duct stones encountered.

The study consisted of routine preoperative cholecystographic examination, duodenal drainage, chemical study of the blood, chemical and bacteriologic examination of bile and stones from the gallbladder and from the common duct, the taking of a postoperative cholangiogram in 8 cases and daily chemical studies of bile from the common duct up to the time the drainage tube was removed from the duct.

Preoperative (Diagnostic) Findings.—The average age of the 21 patients with common duct stone was 60 years, in contrast to an average age of 45 years for patients with dilated common ducts in which no stones were found. Similarly, the duration of symptoms suggestive of disease of the biliary tract was longer in the cases in which stones were

53. Newman, C.: Physiology of the Gallbladder and Its Functional Abnormalities, Lancet **1**:785, 841 and 896, 1933.

present. Biliary colic was a major complaint of 18, or 86 per cent, of patients with common duct stones but had only a 50 per cent incidence in patients with dilatation of the common duct without stones. A history of jaundice was twice as frequent for the patients with common duct calculi as for those without (70 per cent versus 31 per cent) but was sometimes not given for patients with markedly dilated common ducts containing multiple calculi. Dyspepsia was a complaint of all the patients in this series.

Studies of the blood were of little value in differentiating between the patients with stone and those without. A mild elevation of the leukocyte count was frequently associated with the presence of common duct stones but was seldom observed in the absence of stone unless pancreatitis was present. In patients with an elevated icterus index and a positive van den Bergh reaction the value for blood cholesterol was usually elevated above 220 mg. per hundred cubic centimeters. This was seen more frequently in patients with calculous common ducts, for, generally speaking, the icterus index when elevated in cases of calculus was higher than in cases in which calculi were absent. The incidence of an elevated icterus index was higher (81 per cent versus 50 per cent) in the patients with stones in the common duct than in those without.

Duodenal drainage furnished significant diagnostic data. Concentrated bile and clumped crystals of calcium bilirubinate (bile sand) were frequent in patients with common duct stone, whereas a combination of these was seldom found in patients without stones. Chemical determinations of the level of cholesterol in the duodenal bile were not of importance. Usually only a trace (50 mg. per hundred cubic centimeters) of cholesterol was present. Of the greatest differential value was the finding on sterile drainage by the encapsulated method (Twiss [54]) of colon bacilli or streptococci in the drainage. These organisms, singly or together, were present in more than 80 per cent of patients with common duct stones, as against a 34 per cent incidence in patients without stone. Furthermore, cultures yielding these organisms were generally associated with the "bile sand" in patients with stone. Pure cultures obtained from duodenal specimens (only one organism) were common in patients with stone and much less common in those without.

The results of examination of the gastric contents for hydrochloric acid were significant only in that hypochlorhydria was found in all patients with common duct stone, as against a less frequent occurrence in patients without stone.

54. Twiss, J. R.: Technic of Non-Surgical Drainage of the Biliary Tract, J. A. M. A. **100**:792 (March 17) 1933. Twiss, J. R., and Phillips, C. H.: Bacteriological Findings in Disease of the Biliary Tract: An Improved Method of Obtaining Cultures of Bile by Duodenal Drainage, Am. J. Digest. Dis. & Nutrition **2**:663, 1936.

A cholecystogram was taken in the clinic in 23 cases. In no instance was a normally visualizing gallbladder found. Twenty films showed no visualization, and 3 had a faint visualization. The value of the cholecystogram in determining the function of a gallbladder cannot be overestimated, as we have found a 90 per cent agreement between the cholecystogram and the pathologic findings in the cases of over 200 cholecystectomized patients.

Table 1 is a résumé of the preoperative findings in cases of disease of the common duct with and without stones. This study gives presumptive evidence that dilatation of the common duct is often dependent on loss of function of the gallbladder (roentgen evidence) and that

TABLE 1.—*Résumé of Diagnostic Findings in Cases of Disease of the Common Duct With and Without Stone*

	Calculous Common Duct (21 Cases)	Dilated Noncalculous Common Duct (26 Cases)
Diagnostic factors		
Age of patients	50 to 70 years	35 to 50 years
Mean age of patients	60 years	44 years
Total duration of symptoms referable to gallbladder	10 to 40 years	2 to 20 years
Incidence of biliary colic	86%	54%
Incidence of jaundice (by history)	70%	38%
Leukocyte count	Slightly elevated (10,000-14,000)	Normal except with pancreatitis
Icterus index	9+ units in 90%	9+ units in 65%
Duodenal drainage		
Concentrated bile	In duodenum, 65%	In duodenum, 35%
Crystals	Clumped calcium bilirubinate and calcium	Cholesterol crystals
Culture of duodenal contents	Colon bacilli or streptococci in 80%	Mixed or sterile cultures in 70%
Gastric acidity (free)	Achylia or hypochlorhydria in all but 1 case	Various
Cholecystogram	Visualization in only 1 case	Visualization in only 2 cases

this is associated with intermittent spasm of the sphincter of Oddi. The frequent finding of concentrated bile and crystals in drainage of the common bile ducts of patients with nonfunctioning gallbladders is further evidence that the common bile duct may take over some of the concentrating function of the gallbladder and that stasis of bile in the common duct may occur.

The advanced age of the patients, the high incidence of cultures yielding bacteria and the associated hypochlorhydria observed in cases of common duct stone are indicative that prolonged stasis predisposes to stone formation and infection, much as the same train of events previously occurred in the gallbladder. There is no invariable or pathognomonic finding in cases of common duct stone. The history of jaundice, colic and prolonged digestive symptoms in patients in the fifth to the seventh decade of life, a nonfunctioning gallbladder on roentgen examina-

tion and the finding of clumped calcium or calcium bilirubinate crystals associated with colon bacilli or a streptococci are highly presumptive evidence of stone in the common duct.

Findings at Operation.—At operation chemical, bacteriologic and pathologic studies were made of the gallbladder and of bile from the common duct. Table 2 is a résumé of the pathologic changes in the gallbladder as determined by the attending pathologist and of the appearance of the common duct as described by the operating surgeon. The pathologic changes in the gallbladder were in close accord with the results of preoperative cholecystographic examination. Pathologic changes were far advanced in all but 2 cases, and stones were present in the gallbladder in 35 of the 37 specimens.

TABLE 2.—*Macroscopic and Microscopic Pathologic Changes Found at Operation in Patients with Disease of the Common Duct*

	Calculous Common Duct	Noncalculous Common Duct
Disease of gallbladder (attending pathologist's report)		
Chronic cholecystitis and lithiasis	2	7
Severe (ulcerative) cholecystitis with lithiasis	10	8
Acute cholecystitis and lithiasis	1	7
Chronic noncalculous cholecystitis	1	1
No gallbladder (cholecystectomy)	7	3
Total number of cases	21	26
Disease of common duct (operating surgeon's report)		
Dilatation with acute pancreatitis	..	3
Dilatation with chronic pancreatitis	..	6
Dilatation (no other pathologic change noted)	19*	16
Dilatation with acute cholangitis	2	..
Operative injury, stenosis	..	1
Total number of cases	21	26

* In 1 of these cases there was generalized papilliomatosis at the lower end of the common duct.

In 16 instances no cause for the dilatation of the common duct could be ascertained. The appearance of the duct and the degree of associated disease of the gallbladder were the same as those present in the 18 cases of common duct stone in which no other cause for obstruction was observable. The only difference indicated in this group by contrasting findings was that the incidence of cultures yielding bacteria was much lower in the cases in which stones were absent and the duration of disease of the biliary tract, as reflected in symptoms, was much shorter. It was in these conditions (noncalculous) that hypertonicity of the sphincter of Oddi (sphincter spasm) without benefit of the regulatory function of a gallbladder offered the most likely explanation for the dilatation.

Pancreatitis, either acute or chronic, was a probable obstructing factor in 9 patients without stones of the common bile duct. In no case

of common duct stone was pancreatitis deemed present, a finding contrary to that frequently reported in the literature. Stones were frequently found in common ducts which were dilated after a previous cholecystectomy. From this limited series no conclusion can be drawn concerning the incidence of postoperative common duct stones, for exploration of the duct was done only in cases of intermittent jaundice, bile sand and cultures yielding bacteria.

The microscopic, chemical and bacteriologic data on the bile and on the stones from the gallbladders of patients with disease of the common duct are given in table 3. They serve to substantiate the pathologist's report and to add further evidence of the fact that disease of the common duct is a sequel of severe disease of the gallbladder. The findings indicate that the pathologic process in the gallbladder was farther advanced in the patients with common duct stones than in those without.

TABLE 3.—*Chemical, Microscopic and Bacteriologic Findings in the Bile of Gallbladders of Patients with Disease of the Common Duct*

	Calculous Common Duct (14 Cases)	Noncalculous Common Duct (23 Cases)
Bile salts (average)	280 mg./100 cc.	2,000 mg./100 cc.
Cholesterol (average)	211 mg./100 cc.	362 mg./100 cc.
Incidence of crystals	100%	100%
Calcium bilirubinate	7 cases	7 cases
Calcium	6 cases	1 case
Cholesterol	6 cases	9 cases
Incidence of pancreatic ferments	50%	45%
Incidence of cultures yielding bacteria	64%	53%

In all the cases in this series the common duct was dilated at the time of operation. The degree of dilatation was no greater in patients with stone than in patients without stone. It was impossible to determine the original source of the common duct stones, i. e., whether it was the gallbladder, the common bile duct or the hepatic ducts. In only 3 cases were there stones in the common bile duct with the appearance and structure of ordinary "mixed" gallstones. In 16 the stones were composed predominantly of calcium bilirubinate, and in 2 they were pure pigment stones. It is probable that both the calcium bilirubinate stones and the pigment stones were formed in the common duct, as they were in marked contrast chemically and structurally to their associates in the gallbladder.

Bile from the common duct, procured at the time of operation, was examined chemically, microscopically and bacteriologically. The results of the examinations are given in table 4. The patients were, as in the previous studies, divided into those with stone and those without. The results revealed no evidence not previously shown by duodenal drainage.

Common ducts which contained stones showed concentrated bile and concentrated cholesterol more frequently that did ducts without stones. As the patients had nonfunctioning gallbladders in every instance in which the common duct bile was observed before operation to be concentrated, there is little question of the transference of this function to the common duct once the gallbladder is removed by a pathologic process. The ability to concentrate bile was not general in calculous common ducts. Common ducts in which the calculus had produced a long-standing, nearly complete obstruction had a low concentration of bile salts and cholesterol, just as is seen in cases of obstruction (hydrops) of the

TABLE 4.—*Chemical, Microscopic and Bacteriologic Findings in Bile Obtained from the Common Duct at Operation*

	Calculous Common Duct (21 Cases)	Noncalculous Common Duct (26 Cases)
Concentrated bile (800 mg./100 cc. + bile salts)	53%	27%
Bile cholesterol		
50 mg./100 cc. or more	6 cases	4 cases
Less than 50 mg./100 cc.	12 cases	12 cases
Crystals	90%	85%
Calcium bilirubinate	17 cases	9 cases
Calcium	2 cases	1 case
Cholesterol	4 cases	11 cases
None	2 cases	2 cases
Pancreatic ferments		
Present	11 cases	5 cases
Absent	7 cases	7 cases
Cultures	90% positive	58% positive
Colon bacilli	13 cases	5 cases
Streptococci	8 cases	3 cases
Mixed (2 or more organisms)	7 cases	0 case
Sterile	2 cases	10 cases
Other organisms	3 cases	3 cases

gallbladder. When these findings for the operative bile specimens (not concentrated) are correlated with those obtained by postoperative T-tube drainage, it is evident that the role of the liver cannot be overlooked; i. e., in cases of severe obstruction, the liver did not secrete normal bile. The finding of "white" bile (bile containing no cholesterol or bile salts) is evidence that under severe abnormal conditions the common duct may absorb bile salts, pigment and cholesterol.

Pancreatic ferments were more frequently present in the bile of common ducts containing calculi than in that of noncalculous ducts. This could not have been due to the impaction of a stone in the ampulla except in 3 instances. It is apparent that a certain degree of sphincter tone, probably greater than is physiologic, existed, either because of the stones or independently of them. Microscopic examination confirmed

the finding by duodenal drainage of calcium bilirubinate crystals in calculous common ducts and of a variety of crystals in noncalculous ducts. A marked degree of stasis was evident in all of the common ducts exposed.

Cultures of the operative specimens of bile from the common ducts revealed viable organisms in all but 2 calculous common ducts, with colon bacilli and/or streptococci in 75 per cent of all ducts. Only 33 per cent of noncalculous common ducts contained these organisms.

A daily analysis of the bile obtained by T-tube drainage was made in each case. The values for bile salts, cholesterol and ferment concentration were determined, and crystals were noted. In reviewing the results of this extensive chemical study, no evidence as to the functional state of the common duct was obtained except that the bile procured by "free" drainage of the tube was lower in concentration than was that procured after a period of obstruction (clamping) of the tube. As the period of drainage extended and presumably edema and spasm subsided, these variations became less marked, until, apparently with free drainage into the duodenum, no change in concentration existed. The concentration of bile salts from the fistulas of patients with long-continued partial obstruction was generally low. This was true of patients without evident hepatic damage. It is evident that the liver was secreting bile low in bile salt and cholesterol. Such variables as this, as well as spasm or atony of the sphincter, make a specific chemical study of postoperative common duct bile of little value in determining the functional status of the common duct.

A postoperative ("delayed") cholangiogram was taken in 8 cases. In only 1 instance was there evidence of continuing organic obstruction; the patient had papillomatosis of the lower end of the common duct. Five of the patients, however, revealed a functional spasm of the sphincter of Oddi, proved by retention of dye in the common duct with prompt emptying on inhalation of amyl nitrite. This finding of spasm even in such a small series of cases lends support to the theory that the cycle of events we have recorded in our studies may be initiated by spasm of the sphincter and that removal of the results of dysfunction (cholelithiasis, chronic cholecystitis or choledocholithiasis) does not necessarily relieve the patient of the consequences of continuing dysfunction.

The difficulties inherent in a study of the physiology and of the abnormal functions of the common bile duct in cholecystectomized patients are best illustrated by the 2 case histories which follow.

REPORT OF CASES

Case 1.—R. W., a white woman aged 50, was admitted to the hospital with a history of epigastric distress, nausea and vomiting for twenty years. During the five years prior to her admission she had definite episodes of epigastric colic

radiating to the lower angle of the right scapula. On examination she had deep epigastric tenderness.

Laboratory examination showed normal values for blood cholesterol and cholesterol esters. The icterus index was 9. The van den Bergh reaction was negative. The duodenal contents yielded a pure culture of Bacillus coli. The gallbladder did not visualize roentgenographically. Shadows were seen which were interpreted as representing calculi of the gallbladder.

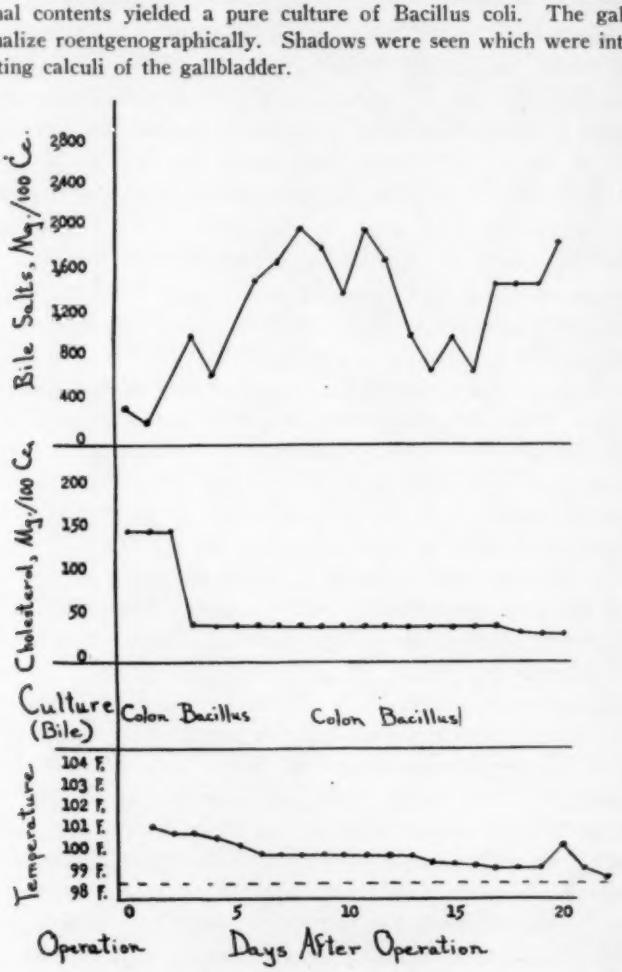

Chart 1.—Temperature and daily determinations of the concentration of bile salts and cholesterol in the common bile duct in case 1.

At operation the gallbladder proved to be functionless (hydrops) and filled with mixed gallstones. The common bile duct was dilated and contained several large calcium bilirubinate stones, different in structure and composition from those found in the gallbladder. Cholecystectomy and choledochostomy were performed. On analysis the bile obtained from the common duct at operation was dilute, containing 310 mg. of bile salts and 50 mg. of cholesterol per hundred cubic centimeters. It contained also clumped calcium bilirubinate crystals, pancreatic ferments of normal activity and colon bacilli.

Comment.—Daily determinations of the composition of the "fistula bile" are recorded in chart 1. The gradual rise in concentration of the bile salts is attributable to an increasing recovery of hepatic function and also in part to the ability of the common bile duct to concentrate bile. The cholesterol content remained relatively constant. Pancreatic ferments and crystals were present in the bile throughout the period of drainage.

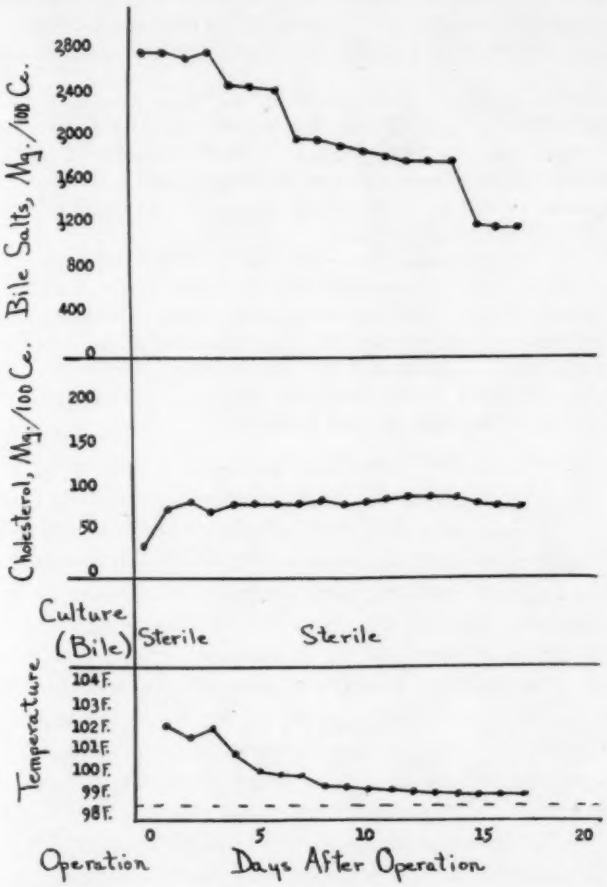

Chart 2.—Temperature and daily determinations of the concentration of bile salts and cholesterol in the common bile duct in case 2.

Cultures of the bile obtained by drainage ten days after the operation showed the continued presence of the colon bacillus infection. A cholangiogram taken on the sixteenth postoperative day showed a normally functioning sphincter of Oddi.

Repeated postoperative studies of material obtained by duodenal drainage have shown a continuing colon bacillus infection of the com-

mon bile duct with alternate dilute and concentrated bile. The patient has been free from symptoms except for rare episodes of mild indigestion. The threat of a recurrent common duct stone is present, and stones may recur if the stasis in the common bile duct is not controlled.

CASE 2.—A white man aged 50 was admitted to the hospital with a history of severe intermittent epigastric pain radiating to the right upper quadrant of the abdomen for five months. He had had jaundice, chills, nausea and vomiting. On examination he showed jaundice, tenderness in the right upper abdominal quadrant and in the epigastrium, a mass in the right hypochondrium and evidence of loss of weight.

Laboratory examination showed the value for blood cholesterol to be 290 mg. and that for cholesterol esters 122 mg. per hundred cubic centimeters. The icterus index was 18.3. The van den Bergh reaction was direct. Duodenal drainage showed concentrated bile, many cholesterol crystals and occasional calcium bilirubinate crystals. A culture of the duodenal contents was sterile. The gallbladder did not visualize roentgenographically.

At operation the gallbladder was totally obliterated, filled with tightly packed "mixed" gallstones. The common bile duct was dilated but contained no stones. The pancreas was normal. Cholecystectomy and choledochostomy were performed. The bile obtained from the common duct was concentrated, containing 2,700 mg. of bile salts and 25 mg. of cholesterol per hundred cubic centimeters. It contained also numerous cholesterol crystals and some calcium bilirubinate crystals. Culture of material from the common bile duct was sterile.

Comment.—Daily determinations of the composition of the "fistula bile" are recorded in chart 2. As the edema in the duct subsided, the concentration of bile salts returned to normal and the stasis, as shown by the crystalline sediment, decreased. The cholesterol content remained at 80 to 100 mg. per hundred cubic centimeters, apparently the concentration being secreted by the liver. Additional cultures of the bile obtained by drainage were sterile. A cholangiogram taken on the nineteenth postoperative day showed a normal sphincter of Oddi, with perhaps a slightly increased tone as shown by a visualization of the pancreatic duct. The dye, however, emptied readily from the duct.

In this patient the disease was of short duration and the dysfunction, dilatation and stasis of the common bile duct followed rapidly on obstruction of the cystic duct and obliteration of the gallbladder. It is probable that had dysfunction of the common bile duct continued for a longer period stone formation and infection would have taken place.

SUMMARY AND CONCLUSIONS

A comparison is made between a series of cases of stone of the common duct and a series of cases of disease of the common duct without stone.

In the majority of cases the common duct stones were not related structurally to the gallbladder stones, and therefore a different cause

must be assumed. In most instances the disease originates in the gallbladder, and with the passage of time the gallbladder becomes obliterated and functionless while the common duct to a greater or lesser degree takes over the concentrating ability of the gallbladder. This is evidenced by the increased concentration of the bile in the common ducts of patients with advanced cholecystic disease.

This concentration of bile is further increased by stasis, which in the presence of gastric achylia predisposes to infection. This combination of factors favors the deposition of bile sand and the formation of calcium bilirubinate stones. As such, common duct stone represents a separate pathologic entity distinct from, though related to and dependent on, the preexisting chronic cholecystitis. The failure of cholecystectomy to break this chain of events probably explains recurrent, as contrasted to overlooked, stones of the common duct.

LYMPHOSARCOMA OF THE STOMACH

GORDON F. MADDING, M.D.
Fellow in Surgery, the Mayo Foundation
AND
WALTMAN WALTERS, M.D., D.Sc.
ROCHESTER, MINN.

The proper classification of tumors arising in lymphoid tissue presents great difficulties. The reports on this subject by Foot,[1] Connor,[2] Oberling[3] and others all show a divergence of opinion and nomenclature. To avoid confusion, then, we shall use in this discussion the classification of sarcomas of the gastrointestinal tract employed by Ewing,[4] namely: (1) spindle cell myosarcoma, (2) miscellaneous round cell or mixed cell alveolar sarcoma and (3) lymphosarcoma.

The spindle cell myosarcoma is likely to be bulky, cystic or solid; it may project into the peritoneal cavity or into the lumen of the stomach; it is noninfiltrating and is late in metastasizing.

Tumors of the miscellaneous round cell type constitute a group about which little is known and for this reason probably do not deserve being classified as a separate variety.

Lymphosarcomas constitute the largest and most important group, of which there are two varieties, differing in the type of cell from which the tumors arise: the reticulum cell sarcoma, arising from the reticulum cells of the germ centers of the follicles and pulp cords, and the malignant lymphocytoma, or small round cell lymphosarcoma, arising from the lymphocytes.

The embryologic origin of the reticulum cell is unknown, but it is certain that neoplastic growths of lymphoid tissue may appear in the

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Division of Surgery, the Mayo Clinic (Dr. Walters).

Abridgment of a thesis submitted by Dr. Madding to the faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirement for the degree of Master of Science in Surgery.

1. Foot, N. C.: Report of a Case of Malignant Endothelioma with Necropsy, J. M. Research **44**:417-430, 1924.

2. Connor, C. L.: Endothelial Myeloma, Ewing: Report of Fifty-Four Cases, Arch. Surg. **12**:789-829 (April) 1926.

3. Oberling, C.: Les réticulosarcomes et les réticulo-endothéliosarcomes de la moelle osseuse (sarcomes d'Ewing), Bull. Assoc. franç. p. l'étude du cancer **17**:259-296 (May) 1928.

4. Ewing, J.: Neoplastic Diseases, ed. 3, Philadelphia, W. B. Saunders Company, 1928.

stomach and by invasion destroy it. Roulet [5] expressed the opinion that lymph nodes possess two types of stroma: one consisting of fibrous connective tissue, from which the true fibrosarcoma or spindle cell sarcoma may be derived, and the other a reticulum cell framework, from which the reticulum cell sarcoma or "retothelsarcoma," as he termed it, may arise. According to Aschoff, Downey and Maximow,[6] the primitive mesenchymal cell of embryonic life is the mother cell for all the types of mature cells which comprise a lymph node.

In this paper an attempt has been made to divide lymphosarcomas of the stomach as nearly as possible into the two types (1) reticulum cell sarcoma (large round cell lymphosarcoma) and (2) malignant lymphocytoma (small round cell lymphosarcoma). An attempt has been made to analyze reticulum cell sarcomas clinically and morphologically and to make some comparisons between them and malignant lymphocytomas. Although this differentiation is not commonly made, it is practical and of clinical importance, for the two types differ in their response to roentgen therapy. According to Krumbhaar [7] and others, the reticulum cell sarcoma shows greater resistance to roentgen therapy than does the malignant lymphocytoma.

To afford a better understanding of the pathogenesis of and the symptoms produced by the reticulum cell sarcoma, we shall sketch briefly the anatomy of the lymphatic vessels of the stomach.[8] The lymphoid tissue in the stomach is much like that of the intestines. The lymphatic vessels arise from a well developed system of capillaries in the most superficial layer of the mucous membrane, between the glands, a layer somewhat deeper than the capillaries of the blood. There is considerable anastomosis throughout the mucous membrane, from which these lymphatic channels extend toward the serosa and form a plexus on the deep surface of the mucosa. From that region the lymphatic vessels extend deeper, through the muscularis mucosae into the submucosa, where the lymph follicles are situated. The lymphatic vessels extend from here through the deep layers of muscles of the stomach and terminate in the retroperitoneal lymph nodes. Each lymph nodule, or follicle, consists of dense groups of lymphocytes supplied by a blood

5. Roulet, F.: (*a*) Weitere Beiträge zur Kenntnis des Retothelsarkoms der Lymphknoten und anderer Lymphoiden-Organe, Virchows Arch. f. path. Anat. **286**:702-732, 1932; (*b*) Das primäre Retothelsarkom der Lymphknoten, ibid. **277**: 15-47, 1930.

6. Aschoff, Downey and Maximow, cited by Hasselmann, C. M.: Retothel-Sarcoma Among Filipinos in the Tropics, Philippine J. Sc. **54**:1-5 (May) 1934.

7. Krumbhaar, E. B.: The Lymphatoid Diseases, J. A. M. A. **106**:286-291 (Jan. 25) 1936.

8. (*a*) Maximow, A. A., and Bloom, W.: A Text Book of Histology, Philadelphia, W. B. Saunders Company, 1930. (*b*) Piersol, G. A.: Normal Histology, ed. 15, Philadelphia, J. B. Lippincott Company, 1932, p. 191.

vessel and surrounded by a framework of connective tissue. In the center of the active follicle is a portion which stains lighter than the rest, the secondary follicle, which is made up of less mature lymphocytes, throughout which are scattered primitive reticular cells with indistinct cytoplasm. While the primary follicle is at rest, the secondary follicle is apparent only as a small artery surrounded by a few nuclei of the primitive reticular cells in the center of the primary follicle.

The material used for study consisted of all specimens of sarcoma of the stomach available for study at the Mayo Clinic. There were 67 such specimens, which could be apportioned as indicated in table 1.

The incidence contained in table 1 is in accord with results of studies made by other authors; however, in some series the classification is so variable that it is difficult to draw comparisons. Most authors concur in the opinion that lymphosarcoma is the most common form of sarcoma found in the stomach. Pack and McNeer [9] expressed the

TABLE 1.—*Types of Sarcomas Represented in Sixty-Seven Cases of Sarcoma of the Stomach Encountered at the Mayo Clinic*

Lesion	Cases	Per Cent
Lymphosarcoma (41, or 62 per cent)		
1. Reticulum cell sarcoma	20	30
2. Malignant lymphocytoma	21	32
Hodgkin's sarcoma	6	8
Leiomyosarcoma	7	11
Fibrosarcoma	9	13
Mixed group	4	6
Total	67	100

opinion that of the two types of lymphosarcoma arising in the stomach practically all lesions are of the reticulum cell variety and only a few are of the malignant lymphocytoma type. Our series shows that the two types are of approximately equal incidence, with the small cell lymphosarcoma (malignant lymphocytoma) in slight preponderance.

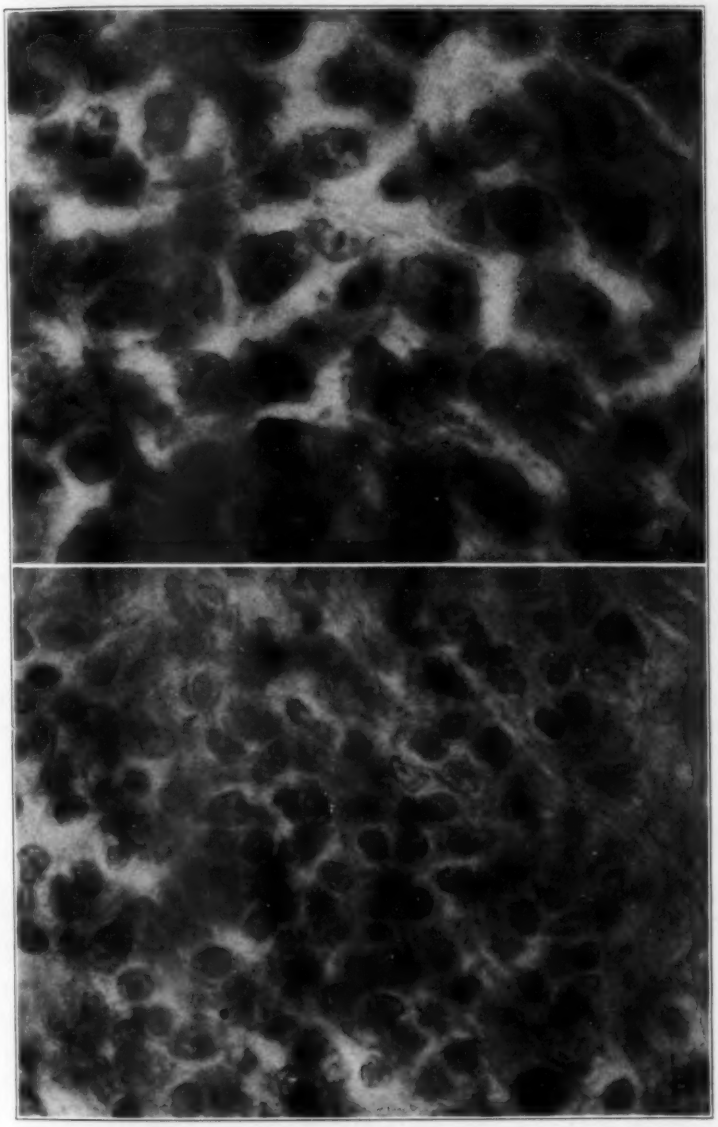
CAUSATIVE BACKGROUND

The cause of lymphosarcoma of the stomach is unknown. We shall not review the speculations that have been offered, and there was nothing derived from this study to add to existent theories.

MORPHOLOGIC ASPECTS

In this series the typical morphologic picture of reticulum cell sarcoma (fig. 1*A*) was one in which the lymph follicles were invaded and destroyed by large, pale cells, with nuclei of bizarre configuration, most

9. Pack, G. T., and McNeer, G.: Sarcoma of the Stomach: Report of Nine Cases, Ann. Surg. **101**:1206-1224 (May) 1935.



A, section of reticulum cell sarcoma of the stomach, with large, pale cells containing nuclei of bizarre configuration. The nucleoli are not prominent, chromatin is finely divided and characteristically the tumor shows a loose cellular structure. Hematoxylin and eosin, × 1,100. *B*, malignant lymphocytoma (small round cell lymphosarcoma), showing wild proliferation of mature lymphocytes. Nucleoli are more prominent and chromatin more heavily distributed than in reticulum cell sarcoma, with a very compact arrangement of the cells. Hematoxylin and eosin; × 1,100.

of which were round, oval, reniform and horseshoe shaped. These nuclei were two to three times the size of those seen in the malignant lymphocytoma (fig. 1 *B*). The cells were larger than immature lymphocytes, and some evidence of phagocytosis was observed. Nucleoli were not prominent, and the chromatin was diffusely dusted throughout the nuclear substance. The cytoplasm was somewhat eosinophilic and was considerable in amount. There was no evidence of formation of reticulum, as determined by the Galantha modification of Bielschowsky's silver impregnation method. Throughout the tumors there were varying numbers of small mature lymphocytes, and the cells were not always uniform in size or shape. Some portions were rather compact, but in most sections the cellular structure was loose. In regions where connective tissue was present, the tumor cells were seen to have their long axes parallel to the long axes of the fibers of connective tissue.

The infiltrative quality of the tumor cells was notable, and the muscular tissues as well as the capsules of the involved lymph nodes were frequently penetrated and destroyed. In some sections, invasion of blood vessels was also noted. The structure of the involved lymph nodes was identical with that of the primary tumor in the stomach.

The absence of reticulum is a characteristic consistent with the observations of Richter [10] and Gall.[11] In reviewing cases of malignant lymphoma of the stomach at the Massachusetts General Hospital, Gall noted the absence of formation of reticulum. It is known that tumor cells do not necessarily carry on the functions of the tissues from which they arise. It has been suggested by Kaufmann and Ribbert [12] that demonstration of reticulum is facilitated by washing out the cells. This procedure, however, could not be followed in any of our studies.

DIFFERENTIAL DIAGNOSIS

Tumors which might be confused with reticulum cell sarcoma are: (1) malignant lymphocytoma, (2) Hodgkin's disease, (3) very cellular carcinoma, (4) endothelioma, (5) hyperplastic noncaseous tuberculosis and (6) giant follicle lymphoma (giant follicle hyperplasia).

The malignant lymphocytoma, or small round cell lymphosarcoma, is a tumor in which the involved lymphoid tissue is destroyed by lymphocytes, usually immature, and in which the capsule and adjacent tissues are invaded. It may or may not be associated with lymphatic leukemia. Usually there is little fibrosis and no eosinophilia. If plasma cells, eosinophils and normal lymphocytes are present, an inflammatory lesion must be considered.

10. Richter, M. N.: Generalized Reticular Cell Sarcoma of Lymph Nodes Associated with Lymphatic Leukemia, Am. J. Path. **4**:285-292 (July) 1928.

11. Gall, E. A.: Personal communication to the authors.

12. Kaufmann and Ribbert, cited by Ewing,[4] p. 414.

The picture seen in Hodgkin's disease is variable, depending largely on the stage of the development of the lesion. Dorothy Reed [13] has established the typical picture as it is known today. Hodgkin's disease is characterized morphologically by marked proliferation of lymphocytes, large and small, and by proliferation of endothelium with the formation of endothelial giant cells, varying numbers of eosinophils, plasma cells and fibroblasts. Early in the disease lymphocytes predominate with an associated endothelial cellular proliferation and some fibroblastic reaction. According to Bunting,[14] the early lymphocytic stimulation is followed by a destructive action on these cells. As the disease progresses, the fibroblastic proliferation increases, and transitions from endothelial cells to giant cells soon occur. These giant cells may be either uninuclear or multinuclear (Sternberg-Reed) giant cells. Eosinophils are seldom absent but are not pathognomonic of this lesion. Bunting maintained that they may occur in any condition in which there is lymphocytic destruction. The 6 cases of Hodgkin's disease of the stomach encountered in this study were reported by one of us (Madding [15]).

At times it is impossible to differentiate absolutely a very cellular carcinoma from a reticulum cell sarcoma. Alveolar and glandular arrangements, the relationship of the long axis of the cells to strands of connective tissue, the presence and size of nucleoli and the presence of mucus in the tumor are factors aiding in this differentiation. When we stained reticulum cell sarcomas by the Galantha method for mucin, we found no evidence of this substance.

Endothelioma of lymphoid tissue at times may be indistinguishable from reticulum cell sarcoma. Although the endothelial cell is ordinarily a large, flat cell with a large, oval nucleus, it may assume many shapes when found in the tumor. The endothelial cells are often found arranged in sheets or cords, and tumors arising from these cells not only are very rare but are much less malignant than sarcomas. There is often a definite relationship of the tumor cells to the endothelium of the sinuses and blood vessels. This tumor is rather radiosensitive and is thus greatly in contrast to the reticulum cell sarcoma.

Chronic hyperplastic noncaseous tuberculosis (Boeck's sarcoid), although rare, may produce symptoms confusing to one attempting a differential diagnosis morphologically. It closely resembles reticulum cell sarcoma, but certain characteristics of the sarcoma, namely, the large endothelial cell proliferation, the presence of giant cells and the absence

13. Reed, D.: On the Pathological Changes in Hodgkin's Disease, with Especial Reference to Its Relation to Tuberculosis, Johns Hopkins Hosp. Rep. **10**:133-196, 1902.

14. Bunting, C. H.: Diseases of the Lymph Glands, in Nelson New Loose-Leaf Medicine, New York, Thomas Nelson & Sons, 1937, vol. 3, pp. 347-368.

15. Madding, G. F.: Hodgkin's Disease of the Stomach: Report of Six Cases, Proc. Staff Meet., Mayo Clin. **13**:618-623 (Sept. 28) 1938.

of lymphocytic hyperplasia, are factors aiding in the diagnosis. In difficult cases resort may be had to inoculation of guinea pigs.

In giant follicle lymphoma there is seen in both the cortex and the medulla a diffuse distribution of the germinal centers composed of pale, uniform cells of uncertain origin. The absence of necrosis, of polymorphonuclear leukocytes and of phagocytosis serves to distinguish the condition from that of a purely inflammatory lesion. Giant follicle lymphoma is a relatively benign form of malignant lymphoma, as shown by the dearth of mitotic figures, and is one of the particularly radiosensitive types of tumors. However, some patients with this lesion present the terminal picture of a patient who has lymphosarcoma.

CLINICAL FEATURES

Age.—Reliance on age of the subjects in studying the incidence of reticulum cell sarcoma of the stomach is as dangerous as in studying that of gastric carcinoma. Reticulum cell sarcoma of the stomach is a disease of later life, the average age of the patients being 46.7 years. Our graphs showed that the peak of the incidence occurs between 40 and 49 years and that 70 per cent of the tumors occur between the fourth and the seventh decade. The youngest patient was 22 years old, and the oldest, 66. These figures agree closely with those for malignant lymphocytoma, with the exception that in graphs of lymphocytoma the peak of incidence is in the sixth decade. In our series the average age for the entire group of patients with sarcoma of the stomach was 50.2 years. Balfour and McCann [16] reported the average age of patients with carcinoma of the stomach as 61—in other words, that there is a difference of 14.3 years between the average age of patients suffering from reticulum cell sarcoma of the stomach and the average age of patients having carcinoma of the same organ.

Sex.—Sex, too, played a part in the incidence of reticulum cell sarcoma, men outnumbering women 6:1. Cheever [17] and Douglas [18] stated the opinion that gastric sarcoma is evenly distributed between the sexes, but throughout the entire group of sarcomas of the stomach reviewed at the clinic tumors among men predominated.

REGIONAL DISTRIBUTION

In the cases which we studied reticulum cell sarcoma was found most often on the lesser curvature and on the posterior wall of the stomach, the regions in which the majority of all malignant lesions of the stomach

16. Balfour, D. C., and McCann, J. C.: Sarcoma of the Stomach, Surg., Gynec. & Obst. **50**:948-953 (May) 1930.

17. Cheever, D.: Clinical Aspects and Treatment of Primary Lymphosarcoma of the Stomach and Intestines, Ann. Surg. **96**:911-923 (Nov.) 1932.

18. Douglas, J.: Sarcoma of the Stomach, with Report of Three Cases, Ann. Surg. **71**:628-636 (May) 1920.

are found. This observation is not in keeping with the opinion expressed by Lubarsch and Henke,[19] that sarcoma seldom occurs on the lesser curvature. The percentages of the commoner sites of occurrence of both reticulum cell sarcomas (large round cell lymphosarcomas) and malignant lymphocytomas (small round cell lymphosarcomas) are contained in table 2.

SIGNS, SYMPTOMS AND LABORATORY OBSERVATIONS

Sarcoma of the stomach presented no typical picture, and only a few of the patients had the classic history for neoplastic involvement of the stomach. A short history presented by a previously healthy person proved more valuable for diagnosis than specific symptoms of a nonmalignant condition. The symptoms, of course, depended on the size and site of the lesion, on the type and extent of the growth and on the patient's reaction to a departure from his normal condition.

TABLE 2.—*Site of Occurrence (by Percentage) of Reticulum Cell Sarcoma and Malignant Lymphosarcoma of the Stomach*

Site	Type of Sarcoma	
	Reticulum Cell, per Cent	Malignant Lymphocytoma, per Cent
Lesser curvature	25	25.8
Posterior wall	25	9.5
Pylorus	15	9.5
Greater curvature	10	4.8
Cardiac portion	10	0.0

According to our observations, the reticulum cell sarcoma arises from the reticular cells of the lymph follicles in the submucosa, spreads from there by permeation and invades the various layers of the stomach. Since the sarcoma originates in the submucosa, the mucosa itself is not early involved and ulceration does not occur in sarcoma of the stomach as soon as it does in carcinoma of the stomach. Because of the proximity of the sarcoma to the submucous plexus of nerves, pain is a very common feature. In all the cases of reticulum cell sarcoma studied, pain was present, either generalized throughout the abdomen or, more often, localized in the midepigastrium. In some instances the history was like that typical of peptic ulcer. The pain, however, did not respond as well to the usual treatment of ulcers and was not periodic, as that of ulcers often is. Some patients complained of belching, anorexia, epigastric nocturnal pain and loss of weight and strength. Six of the 21 patients complained of vomiting, which in 3 instances was caused by involvement of the pylorus by the neoplasm. In 1 case only was gross

19. Lubarsch, O., and Henke, H.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1926, vol. 4, pt. 1.

blood noted in the stool. Reticulum cell sarcoma does not show large masses projecting into the leaves of the omentum or into the free peritoneal cavity, as fibrosarcoma and leiomyosarcoma. Consequently, a palpable tumor was not often found.

The duration of symptoms of reticulum cell sarcomas ranged from two months to several years, but as a rule the course was shorter than that of malignant lymphocytoma or carcinoma. The average duration of symptoms of reticulum cell sarcoma in inoperable patients was thirty-seven months. In 20 per cent of the cases the family history indicated a background of malignancy. Although there was always loss in weight, it varied in amount, the mean loss being 25 pounds (about 11 Kg.).

Gastric analysis (Töpfer's test) showed achlorhydria in 67 per cent of the cases of reticulum cell sarcoma; normal acids in 20 per cent, and free acid but in subnormal amounts in 13 per cent. The blood picture was of the type associated with other tumors involving the stomach, but the anemia was not as extreme as it is in the presence of carcinoma of the stomach. This is perhaps due in part to delayed ulceration of the sarcomatous lesions. The anemia that we observed was of the microcytic hypochromic type, with a hemoglobin content averaging 84 per cent and a mean erythrocyte count of 4,500,000. The leukocyte counts were normal, averaging 8,200. There were not sufficient differential determinations of leukocytes from which to form any conclusions. (It is interesting to note that in 1 instance an associated lymphatic leukemia was found to afflict a patient who had generalized reticulum cell sarcoma of the lymph nodes.) The temperature was normal in all cases but 2, in which readings of 99 and 99.6 F. were recorded at the time of the initial examination.

DIAGNOSIS BY ROENTGEN EXAMINATION

Since roentgen examination failed to lead to the correct diagnosis in any of the cases, it seems reasonable to conclude that roentgenographically there are no absolutely diagnostic characteristics of the lesion. The roentgen diagnosis most often made was "carcinoma," but the roentgenographic examination was important as giving an index to the operability of the lesion. Holmes, Dresser and Camp [20] expressed the opinion that there is nothing diagnostic in the roentgenographic appearance of lymphosarcoma of the stomach, but said that in some cases of lymphosarcoma peristalsis is not interfered with as much as in most cases of carcinoma of the stomach. This group of reticulum cell sarcomas of the stomach were diagnosed by roentgen examination as carcinoma in 15 cases and as ulcer in 2 cases. The condition was pro-

20. Holmes, G. W.; Dresser, R., and Camp, J.: Lymphoblastoma, Radiology 7:44-50 (July) 1926.

nounced normal in 1 case and in 2 cases no examination was made. According to Schlesinger,[21] a stomach involved by sarcoma will not dilate during insufflation, but there is no reason to believe that a stomach diffusely involved by scirrhous or mucous carcinoma would dilate under similar circumstances.

METASTASIS

The manner and route of dissemination of reticulum cell sarcoma depend largely on the location of the tumor in the stomach. The spread is achieved usually by the lymphatic system, but we observed evidence of invasion of the blood vessels in some sections. Because the sarcoma often occurs on the lesser curvature of the stomach, the lymphatic vessels which drain toward the liver are usually involved after the perigastric lymph nodes have been invaded. Metastatic lesions occurred in 65 per cent of the cases of reticulum cell sarcoma and in 70 per cent of the cases of malignant lymphocytoma. Flebbe[22] gave the following list to show the order of frequency in which the various organs are affected by metastasis: regional lymph nodes, liver, mesentery, colon, peritoneum, omentum, ovary, pancreas, bones, pleura, lung, testicle, spleen, diaphragm, kidney, adrenal and skin.

TREATMENT AND PROGNOSIS

Surgical treatment has more to offer to patients having sarcoma of the stomach than to those having carcinoma. Until the advent of radiation therapy, the treatment was the same for the two conditions, namely, an attempt at radical extirpation. Our studies showed that of patients with reticulum cell sarcoma 90 per cent resorted to operation; of those with malignant lymphosarcoma, 66 per cent. Among patients having both types of lymphosarcoma encountered at the clinic, the percentage of operations was higher than among patients having carcinoma of the stomach, according to Ranschoff and Dickson.[23] The patients whose reticulum cell sarcoma was treated by surgical procedures alone had an average life span of three and thirty-eight hundredths years, as contrasted with three and thirty-one hundredths years for those on whom radiation therapy was used as an adjunct. In neither of these groups were patients included who died of postoperative complications (pneumonia, peritonitis and embolus). Of the entire group of patients who had reticulum cell sarcoma of the stomach and who were treated at the clinic, 41 per cent are still living; the longest survival period for any

21. Schlesinger, H.: Unterscheidet sich das Magensarkom klinisch von Karzinom? Wien. klin. Wchnschr. **29**:785-791, 1916.

22. Flebbe, G.: Ueber das Magensarkom, Ztschr. f. Path. **12**:311-336, 1913.

23. Ranschoff, J. L., and Dickson, T. R.: Sarcoma of the Stomach, Ann. Surg. **97**:68-73 (Jan.) 1933.

patient in this group was fifteen years at the time the person was last heard from. The duration of life was directly related to the presence or absence of involvement of the lymph nodes. As with carcinoma, the grade of malignancy of the tumor and the amount of involvement of lymph nodes, which closely parallels the malignancy, were the two important factors in determining the prognosis. Of the reticulum cell sarcomas, 65 per cent were found at the time of operation to have involved the lymph nodes. The life span of the group of patients with such involvement was two and seventy-nine hundredths years, as compared with four and eight-tenths years for the group of patients having no involvement of the lymph nodes. Age and sex played no part in the prognosis for this group.

In comparing the figures for the group of patients having reticulum cell sarcoma with those for the group having malignant lymphocytoma, one finds that the latter have the better life expectancy. The patients having malignant lymphocytoma who were treated by surgical means alone had an average life of five and six-tenths years postoperatively, as contrasted with three and sixty-five hundredths years for those treated by surgical intervention followed by irradiation. Of the patients with malignant lymphocytoma, 56 per cent were still living when last heard from. Two of these patients were living and well fourteen years after their operation. One died seven years postoperatively of pyelonephritis; at necropsy no evidence of the tumor was found. For only 1 of the patients, who achieved a fourteen year cure, was roentgen therapy used in addition to a surgical procedure.

From the aforementioned statistics, one obtains the impression that a patient having malignant lymphocytoma (small round cell lymphosarcoma) has a better prognosis than does a patient having reticulum cell sarcoma. This idea conflicts with the opinion expressed by Jackson,[24] who, in a general discussion of the lymphomatoses of the body without special reference to the stomach, said that reticulum cell sarcoma remains localized for a longer period than malignant lymphocytoma and that prompt surgical removal makes possible a longer survival for some patients.

On the reactivity of the two types of tumor cells to roentgen therapy, there seems to be some uniformity of opinion. Krumbhaar [7] and Lalung-Bonnaire and Bablet [25] stated the opinion that reticulum cell sarcomas are more resistant to this form of therapy than are malignant lymphocytomas. In the cases of reticulum cell sarcoma of the stomach encoun-

24. Jackson, H.: The Classification and Prognosis of Hodgkin's Disease and Allied Disorders, Surg., Gynec. & Obst. **64**:465-467 (Feb.) 1937.

25. Lalung-Bonnaire and Bablet: A propos des sarcomes ganglionnaires du cou: les tumeurs d'origine réticulo-endothéliales, Presse méd. **2**:1194 (Sept. 5) 1925.

tered at the clinic roentgen therapy seemed to play no part in increasing the life expectancy. This seemed true also in the group of patients having malignant lymphocytoma; in that group the patients given only surgical treatment lived an average of one and ninety-five hundredths years longer than those given both surgical and roentgen therapy. However, of the patients receiving both surgical treatment and roentgen therapy, 83 per cent had glandular involvement. Of the patients having malignant lymphocytomas and receiving only surgical treatment, only 65 per cent had glandular involvement. Thus, one may see that the group of patients to whom roentgen therapy was given as a supplement to surgical treatment had from the beginning a poorer prognosis, because of the more extensive involvement.

Of the group of patients having malignant lymphocytoma, 6 were found to be inoperable. On 3 of them roentgen therapy was used, with the result that 1 patient was living and well two and one-half years after the roentgen therapy was given and the other 2 lived an average of two and two-tenths years. The other 3 patients with inoperable malignant lymphocytoma, who did not receive any form of treatment, were dead within four months.

Of the 2 patients having reticulum cell sarcoma which was found to be inoperable, 1 was given roentgen therapy and died on the way home; the other, who received no treatment, died four months postoperatively, of hemorrhage.

Another interesting feature of our series was the comparison of the prognosis for reticulum cell sarcoma and malignant lymphocytoma with that of other sarcomas of the stomach. According to D'Aunoy and Zoeller,[26] pedunculated or spindle cell sarcoma, with which they included leiomyosarcoma and fibrosarcoma, has a better prognosis than the infiltrating type of sarcoma, which includes the reticulum cell sarcoma and the malignant lymphocytoma. This was not true of the group of sarcomas encountered at the clinic. In our series the average life span for patients having spindle cell sarcoma was three and three-tenths years, only 1 patient being inoperable at the time of exploration. The average life span of patients having reticulum cell sarcoma and malignant lymphocytoma was three and ninety-eight hundredths years.

These observations are supported by the opinions expressed by Jones and Carmody [27] and also by Collins,[28] all of whom found that

26. D'Aunoy, R., and Zoeller, A.: Sarcoma of the Stomach: Report of Four Cases and Review of the Literature, Am. J. Surg. **9**:444-464 (Sept.) 1930.

27. Jones, T. E., and Carmody, M. G.: Lymphosarcoma of Stomach: Report of Case with Nineteen-Year Surgical Cure, Ann. Surg. **101**:1136-1138 (April) 1935.

28. Collins, E. N., and Carmody, M. G.: Lymphosarcoma of Stomach: Report of Four Cases, Am. J. Digest. Dis. & Nutrition **3**:884-888 (Feb.) 1937.

patients having round cell lymphosarcoma comprised the greatest number of those surviving the five year period. The case reported by Jones and Carmody was one of lymphosarcoma of the stomach; the patient was living and well nineteen years postoperatively—the longest survival period of any patient having sarcoma of the stomach reported in the literature.

Among the patients encountered at the clinic, 56 per cent of those who had malignant lymphocytoma are still living, as compared with 41 per cent of those who had reticulum cell sarcoma. Eighteen per cent of the patients who had leiomyosarcomas are still living, and 62 per cent of those who had fibrosarcomas. The number of patients in this series is perhaps too small to permit formation of any statistical conclusions.

In connection with this consideration of the results obtained in treating with roentgen therapy patients having inoperable lymphosarcoma, it is interesting to note the classic experimental work of Heineke,[29] who demonstrated well the effect of radiation on various tissues of the body. Numerous animals were irradiated for varying periods and then killed; sections of all tissues were immediately made. It was the lymphoid tissue which responded first and most markedly to this irradiation. The lymphocytes bordering the follicles were the first to disintegrate, and these were replaced by epithelial cells. The clear, large cells in the center of the lymph follicles did not disintegrate, but seemed to become phagocytic. These epithelioid cells were of questionable origin. Heineke stated the belief that they were derived from the supporting structure of the lymph node. Ribbert, Zeigler and Kaufmann[30] declared that they were transformed endothelium of the supporting tissue of the lymph node. Councilman, Mallory and Pearce[31] said that they were proliferated endothelium of the reticulum.

COMMENT

Review of the cases of reticulum cell sarcoma and malignant lymphocytoma encountered at the Mayo Clinic confirms the general impression that lymphosarcoma is an uncommon condition but contrasts with the general opinion that the two tumors have a better prognosis than leiomyosarcoma and fibrosarcoma. Reticulum cell sarcoma and malignant lymphocytoma are as insidious in their development as carcinoma, and neither lesion seems to offer a greater probability of reaching the surgeon in an early and operable stage.

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29. Heineke, H.: (*a*) Experimentelle Untersuchungen über die Einwirkung der Röntgenstrahlen auf innere Organe, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **14**: 21-94, 1905; (*b*) Ueber die Einwirkung der Röntgenstrahlen auf Tiere, München. med. Wchnschr. **50**:2090-2092 (Dec. 1) 1903.

30. Ribbert, Zeigler and Kaufmann, cited by Heineke.[29a]

31. Councilman, Mallory and Pearce, cited by Heineke.[29a]

In the stomach, the radical operability was low, and differential diagnosis to distinguish lymphosarcoma from carcinoma was impossible. On the basis of the histories at the clinic, it seemed safe to conclude that both reticulum cell sarcoma and malignant lymphocytoma remain localized for some time. Thus, a radical cure by total extirpation is possible, and this should be the goal in every instance.

It seemed evident from the malignant lymphocytomas which were found to be inoperable that irradiation played a part in prolonging the life of the patients. This, however, was not true of the inoperable reticulum cell sarcomas, of which there were only 2. It would seem, on the strength of this survey of a group of patients having sarcoma of the stomach, that it is highly desirable and practicable to perform an exploratory operation and to obtain a biopsy specimen, even for patients concerning whom the clinical evidence points strongly to the presence of an inoperable growth. A differentiation of the two types of so-called lymphosarcoma may then be made, and patients having malignant lymphocytoma (small round cell lymphosarcoma) may be given the benefit of roentgen therapy.

Borzell [32] suggested the use of radiation therapy for patients with lesions clinically found to be inoperable, with the hope of reducing the size of the lesion in a certain percentage of cases. In other words, preoperative intensive irradiation probably would convert an inoperable lesion into one in the stage of operability. Above all, it seems important to differentiate the two types of lymphosarcoma, so that adequate evidence may be accumulated as to the exact histologic type of neoplasm which can be benefited by roentgen therapy.

CONCLUSIONS

Sixty-seven cases of sarcoma of the stomach were studied, of which group 30 per cent were cases of reticulum cell sarcoma (large round cell lymphosarcoma) and 32 per cent of malignant lymphocytoma (small round cell lymphosarcoma).

Morphologically, reticulum cell sarcoma is characteristic. The typical cells are large and pale, with nuclei of bizarre configuration, most of which are round, oval, reniform or horseshoe shaped. Nucleoli are not prominent, and the chromatin is diffusely dusted throughout the nuclear substance. There is no evidence of formation of reticulum.

Conditions which might be confused morphologically with lymphosarcoma are: (1) malignant lymphocytoma, (2) Hodgkin's disease,

32. Borzell, F. F., in discussion on Drane, R.: A Brief Consideration of Sarcoma of the Stomach: Report of a Case of Primary Lymphosarcoma, Am. J. Roentgenol. **34**:757-758 (Dec.) 1935.

(3) very cellular carcinoma, (4) endothelioma, (5) noncaseous tuberculosis and (6) giant follicle lymphoma.

Clinically, it is impossible absolutely to differentiate reticulum cell sarcoma from other neoplastic lesions involving the stomach.

Treatment of lymphosarcoma of the stomach should be surgical removal when possible, with roentgen therapy used as an adjunct in the treatment of the malignant lymphocytoma.

Prognosis for the combined group of lymphosarcomas of the stomach is better than it is for carcinoma involving this organ. The entire group of lymphosarcomas of the stomach observed by us had a better prognosis than did the group of leiomyosarcomas and fibrosarcomas.

It is practicable to differentiate the two types of lymphosarcoma of the stomach, because of the morphologic variation and also because if differentiation is made, adequate evidence may be accumulated as to the exact histologic type of neoplasm which may be benefited by roentgen therapy.

PRIMARY CARCINOMA OF THE TERMINAL PORTION OF THE COMMON BILE DUCT

B. PINES, M.D.
AND
J. RABINOVITCH, M.D., C.M.
BROOKLYN

It is proposed to present in this paper some of the salient features of carcinoma of the terminal portion of the common bile duct with special reference to its pathologic picture and atypical symptoms. The following observations are based on 17 cases of carcinoma of this area collected from the records of the Jewish Hospital. In 8 of these cases necropsy was performed, which allowed us a more detailed study of the pathologic changes. Analysis of the case histories was instigated by the considerable literature on the subject which has accumulated within recent years, and some of the striking features that became manifest from this analysis are the following interesting facts: first, the discovery in a relatively large percentage of cases of an acute inflammatory process of the gallbladder as the outstanding characteristic at or about the time of the first examination; second, the frequent finding of concomitant changes in organs adjoining the bile duct, which gave rise to symptoms that overshadowed at times those produced by the primary lesion in the bile duct and rendered clinical diagnosis difficult.

It is not within the scope of this paper to review in detail the etiology, pathology and symptoms of carcinoma of the bile duct, as this information is readily available in any of the numerous publications on the subject, but rather to discuss a few of the more salient factors which should be borne in mind when one is called on to treat this condition. An analysis of the voluminous literature on carcinoma of the bile duct has been presented in an admirable paper by Lieber, Stewart and Lund.[1] The historical phase, therefore, has been deleted from this paper.

We wish to state at the outset that the present study is concerned with neoplasms confined to the terminal portion of the common bile duct, including the ampulla and the papilla of Vater. It is not concerned with lesions arising from the duct above the duodenum or with tumors arising from the duct of Wirsung or the duodenum.

From the Department of Surgery and the Department of Pathology, the Jewish Hospital.

1. Lieber, M. M.; Stewart, H. L., and Lund, H.: Carcinoma of the Peripapillary Portion of the Duodenum, Ann. Surg. **109**:383 (March) 1939.

The clinical manifesations of carcinoma of the terminal portion of the bile duct are subject, by reason of the anatomic peculiarities of the part, to many variations. The close proximity of the duodenum to the bile duct and the close anatomic relation which exists between the pancreas, liver and gallbladder as their ducts meet in this narrow zone of the bile duct is responsible for the secondary pathologic changes and clinical complications that are apt to occur in cases of this condition. The same anatomic relation of these structures permits a great variety of symptom complexes even in the presence of a trivial lesion in the duct. It is well to bear in mind also that the site in which symptoms first appear is not necessarily that in which the disease develops. Thus, a growth situated at the point of entry of the common bile duct and the pancreatic duct into the ampulla causes interference with the outflow of biliary and pancreatic secretions into the duodenum; this in turn gives rise to far-reaching pathologic changes in the liver, gallbladder and pancreas and causes symptoms peculiar to the organ thus affected. Occasionally, too, the growth in the duct is accompanied by calculous deposits in the biliary and pancreatic ducts, or the ductal growth may invade the duodenum and cause necrosis and ulceration of its wall. Such complicating factors give rise to a rather misleading clinical picture and render diagnosis difficult. In summary it may be said that the symptoms of carcinoma of the terminal portion of the bile duct are not entirely dependent on factors inherent in the growth itself but are influenced also by a variety of other factors, the most important of which are the anatomic configuration of the part affected, the type and location of the tumor, the extent of dissemination of the tumor and the secondary inflammatory changes which so often form part of the pathologic picture.

AGE AND SEX

The ages of the patients in this series ranged from 38 to 68, averaging 56.5. These figures are in accord with the records collected from the literature, and they are also in harmony with the general incidence of cancer of any organ of the body. There were 12 men and 5 women, a ratio of approximately 2:1.

ANATOMIC CONSIDERATIONS

As carcinoma of the bile duct is closely related to the histologic structure of the duct, it will be necessary to restate the cardinal features of the old and new concepts of its minute anatomy, with special emphasis on these aspects that are relevant to the purpose of this paper.

Kiernan,[2] as early as 1833, first described accessory glandlike structures within the walls of the bile ducts which communicate with

2. Kiernan, F.: The Anatomy and Physiology of the Liver, Phil. Tr., London **123**:711, 1833.

the lumen by numerous minute orifices. Several years later, Theile [3] showed that these structures consist of branching clusters terminating frequently in small cecal diverticula; he considered them to be small mucous glands. Beale [4] was the first to use the term parietal saccule for the mucous glands of Kiernan and Theile; he considered them ductal diverticula rather than mucous glands and found that they occurred not only in the common and hepatic bile ducts but within the smaller ramifications of the intrahepatic bile ducts. In most textbooks on histology these saccules are referred to as glands of the ducts. From a number of serial sections of the normal distal portion of the common bile duct which we recovered at necropsy shortly after death, the only structures present in the walls of the ducts which might be interpreted as mucous glands are the parietal sacculi. These structures, when sectioned at levels not showing their communication with the lumen of the main duct, resemble glandular elements. According to Cox,[5] they are not to be considered as true glands, for both anatomic and physiologic reasons. He showed that in the case of biliary obstruction of whatever cause these sacculi dilate in the same fashion as do the bile ducts and that their epithelial lining exhibits the same fat-absorptive property as does that of the epithelium of the bile ducts and gallbladder. This investigator concluded, therefore, that there are no such structures as true mucous glands of the bile ducts. It is true that their epithelium secretes mucus, but the same holds true in the case of epithelium of the ducts and of the gallbladder. Besides, they never contain mucus in any greater amount than do the cells covering the main ducts and the gallbladder (fig. 1).

The view held by Cox is analogous to the view we have expressed, although we seem to differ in one respect, namely, that in addition to the aforementioned changes we have noted in the normal bile duct villous structures which project from the surface mucosa into the lumen. As we understand, or perhaps misunderstand, the conclusions of Cox, similar villus-like folds were described by him to be present only in pathologic bile ducts; he considered them to be the walls or lips of dilated sacculi which appear in cases of biliary obstruction.

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3. Theile: Die Leber, in Wagner, R.: Handwörterbuch der Physiologie, Braunschweig, F. Vieweg u. Sohn, 1842-1853, vol. 2, pp. 349-351.

4. Beale, L. S.: On Some Points in the Anatomy of the Liver of Man and Vertebrate Animals, London, John Churchill, 1856, pp. 31-80; Lectures on the Principles and Practice of Medicine: The Liver, London, J. & A. Churchill, 1889.

5. Cox, F. W.: Changes in the Bile Ducts and Parietal Sacculi Following Absence of the Gall Bladder, Surg., Gynec. & Obst. **55**:168 (Aug.) 1932.

PATHOGENESIS

The following observations are based on a series of 8 cases of carcinoma of the terminal portion of the common bile duct in which necropsy was performed. Grossly, the tumor was either a small, soft, friable papillary lesion or a firm, nodular growth which caused partial or complete obstruction of the bile duct. The sectioned surfaces were usually gray. The size of the tumor was determined in all 8 cases, the largest growth measuring 4 by 3 cm. and the smallest 5 mm. in

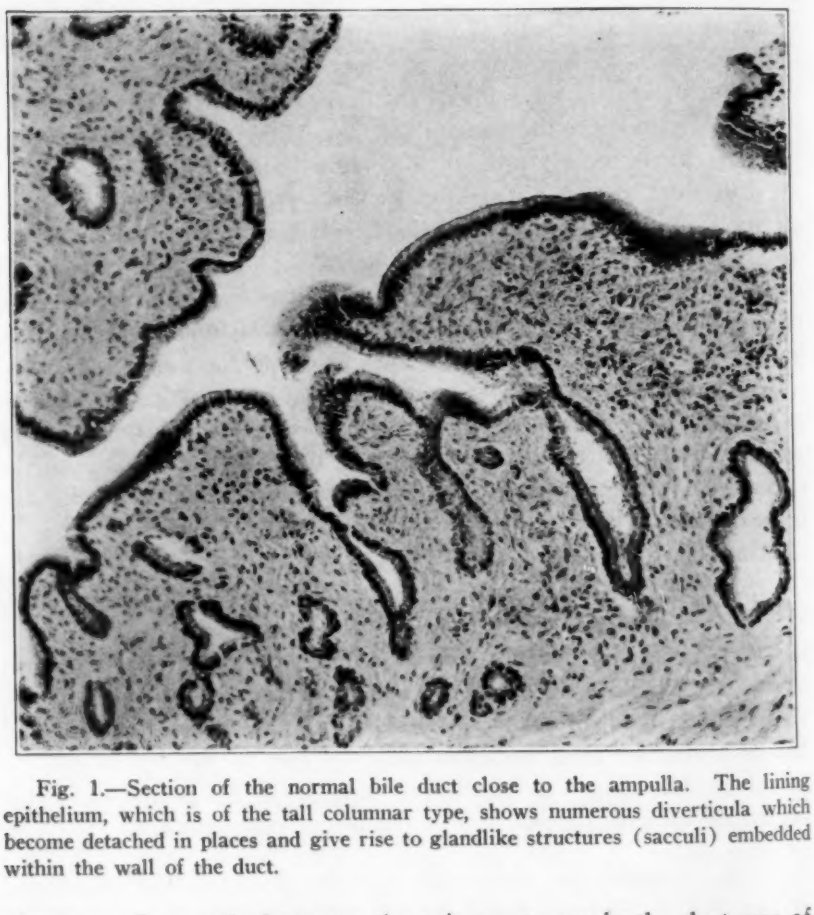

Fig. 1.—Section of the normal bile duct close to the ampulla. The lining epithelium, which is of the tall columnar type, shows numerous diverticula which become detached in places and give rise to glandlike structures (sacculi) embedded within the wall of the duct.

diameter. In certain instances the primary tumor in the duct was of insignificant size and appearance, yet its invasion into adjoining structures, such as the duodenum, was extensive. It was difficult to decide in these cases which was the primary and which the secondary lesion. The size of the tumor was not conclusive evidence, for a secondary growth may be larger than the primary growth. In 1 instance a

primary carcinoma of the ampulla was erroneously diagnosed as primary in the duodenum, but microscopic examination of the specimen proved it to be of ductal origin. The symptoms of carcinoma of the two organs are similar, although carcinoma of the ampulla probably gives rise to symptoms earlier than does a lesion of the duodenum.

In only 1 of the 8 cases was the ampulla sufficiently dilated to allow free escape of bile into the duodenum. When the growth had caused partial or complete blockage to the outflow of bile there occurred various degrees of dilatation of the biliary channels, including the gallbladder. In 1 case the common bile duct was so dilated as to be mistaken at first sight for the gallbladder. Accompanying the dilatation of the ducts there was generally found an associated inflammatory reaction.

Microscopically, all the tumors stained with hematoxylin and eosin showed a strikingly morphologic similarity to the normal parietal sacculi lying within the wall of the bile duct. The epithelium of the growth was in general of the tall columnar type, and the structure was that of an adenocarcinoma. There were acini and tubules lined by columnar cells and set in a stroma of relatively dense fibrous connective tissue. Evidence of secretory activity of these cells was furnished by the presence of mucin within the cellular cytoplasm and within the acini. Many of the cells contained small droplets of mucin in their cytoplasm, and some of them were swollen to signet ring shape by a large globule of this substance, which distended the cell and forced the nucleus to one edge. A cell thus distended may burst, discharging its mucinous content into the lumen or into the connective tissue spaces (fig. 2).

In most cases the cells were obviously malignant, but in others the appearance was not greatly different from that of the normal cells of the mucosa and the parietal saccules. In cells free of mucin the nuclei were relatively large, deeply stained and basally placed, leaving a peripheral, somewhat palely stained granular cytoplasm. Mitotic figures were relatively few, which designated a low degree of malignancy. The stroma was irregularly distributed amidst the various epithelial structures and was infiltrated with various amounts of inflammatory cells. In certain cases the tumor showed extensive necrosis, and this was usually associated with a marked inflammatory reaction.

The close similarity in both architectural pattern and secretory activity of the tumor cells to those of the parietal sacculi is striking and at once suggests a genetic relation. We are thus of the opinion that these tumors of the bile duct probably have their origin from the parietal sacculi lying within its wall.

In the great majority of cases carcinoma of the bile duct spreads by direct invasion of the neighboring viscera and the regional lymph nodes. The growth is rarely disseminated to distant organs even in its terminal

phase. Early in its course, however, it invades locally and understeps the limits of successful removal. The duodenum is generally the first organ to be involved. It was involved in 5 cases of the present series in which autopsy was performed. Invasion into the duodenum takes place in the deeper layers of its wall, the mucosal surface remaining unaffected as a rule. However, when the duodenal mucosa is also part of the tumor process, the clinical features may suggest a primary tumor of the duodenum rather than of the papilla. This occurred in 2 cases of

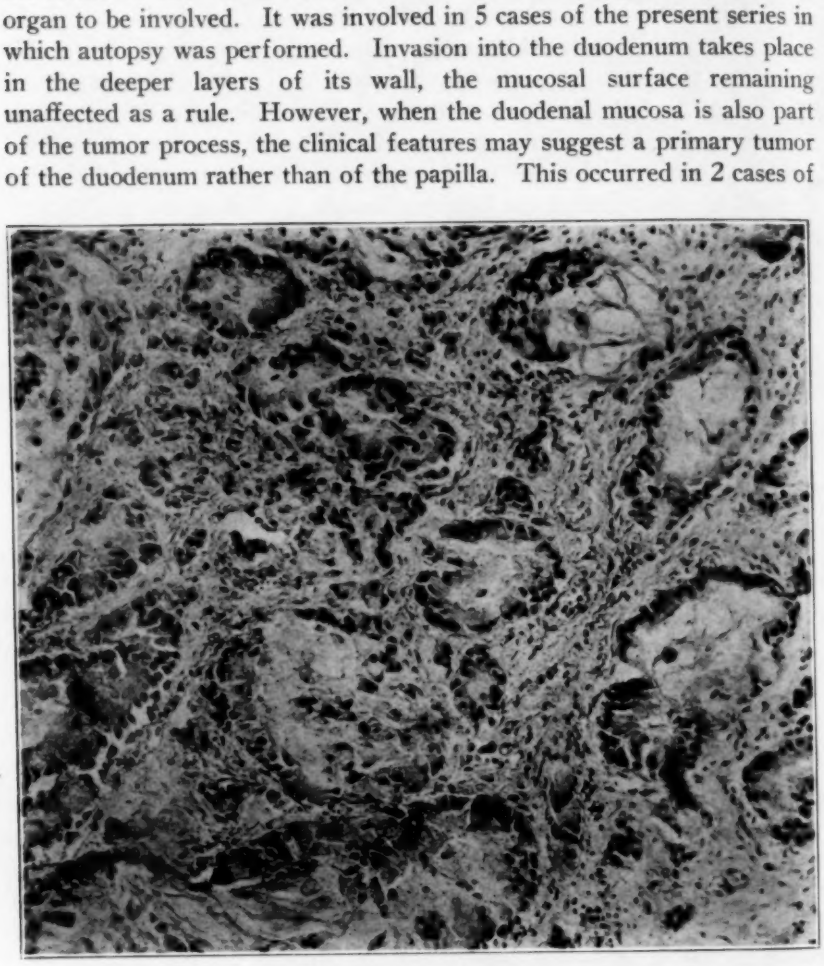

Fig. 2.—Adenocarcinoma of the terminal portion of the bile duct. Note the glandlike structure of the growth and the presence of mucus both within the cells and within the lumens.

our series; in each case it was associated with extensive necrosis, ulceration and secondary infection of the duodenal wall.

Direct extension of the growth into the pancreas occurred in 2 cases. In 1 the duct of Wirsung was obstructed, and this was associated with fat necrosis and a diffuse inflammatory process of the pancreas. In another similar obstruction of the pancreatic duct there were multiple abscess formations within the gland.

The liver showed evidence of biliary obstruction characterized by biliary and saccular dilatation, round cell infiltration and fibroblastic proliferation.

The gallbladder showed particularly interesting changes. In 2 cases it was the seat of an acute suppurative process, and in 4 others it showed evidence of empyema. The mechanism responsible for the lesion in the gallbladder may be explained perhaps on the basis of an ascending infection from the infected tumor in the bile duct and adjoining duodenum. In all likelihood, however, the inflammation of the gallbladder was part of the general cholangitis secondary to biliary obstruction. The nature of this complicated mechanism is of fundamental importance to a proper understanding of the etiology and a proper interpretation of the symptoms of suppurative cholecystitis which complicate obstruction of the biliary duct. When suppuration of the gallbladder occurs it gives rise to clinical symptoms which usually overshadow the primary lesion in the duct. Many patients with carcinoma of the bile duct are first brought to the attention of the surgeon because of the acute fulminating process in the gallbladder, and at operation empyema of the gallbladder is found. Should the patient recover from the operation, he usually succumbs soon after from the effects of the neoplasm in the duct.

The regional lymph nodes are involved about as often as is the duodenum, and their involvement may preclude successful operation in cases in which extirpation of a localized mass might otherwise be contemplated. In this series the regional lymph nodes were involved in only 2 of the cases in which necropsy was done. Distant metastasis is uncommonly observed, even at autopsy. It occurred in none of our cases.

SYMPTOMS

The onset of symptoms was acute in 10 cases and insidious in 7. The earliest treated patient dated the onset of his illness back to three weeks prior to hospitalization, the latest eighteen months, giving an average duration of symptoms of five and two-tenths months. An analysis of the various symptoms showed that jaundice occurred in 16 cases, in 10 of which there was progressive and in 6 of which there was intermittent icterus. Loss of weight occurred in 12 patients, anorexia in 10, vomiting in 5, pain in the right upper quadrant of the abdomen in 7, dyspepsia (i. e., epigastric distress, eructation, flatulence and heart burn) in 9, chills and fever in 4, weakness in 3, intolerance to fat in 2, diarrhea in 1 and fainting and hematemesis in 1. In addition to the aforementioned symptoms, light-colored stools and dark urine were observed by 14 of the patients and tarry stools by 2.

The outstanding physical findings consisted essentially of the following: icterus, 16 cases; dermatitis factitia, 4 cases; purpuric spots, 2

cases; pallor, 2 cases; cachexia, 1 case; malnutrition, 1 case; a large, palpable, firm liver (from 2 fingerbreadths below the costal margin to the level of the umbilicus), 15 cases; hepatic tenderness, 3 cases; general abdominal tenderness, 3 cases; spasm over the upper right quadrant of the abdomen, 2 cases; tenderness and spasm over the gallbladder, 2 cases; distention, 3 cases, and ascites, 1 case.

Laboratory studies yielded the following findings: The urine showed the presence of bile in 14 cases. Urobilinogen was absent in 4 cases; tyrosine crystals were present in 1 and no leucine crystals in 1. Amylase was absent in 1.

The icterus index of the blood was elevated in 11 cases; the lowest value was 31.2 and the highest 225, with an average of 112 for the series studied. The van den Bergh test showed a direct immediate positive reaction in 9 cases and a biphasic reaction in 1. The sugar content was elevated in 6 cases, the values ranging from 125 to 174 mg. per hundred cubic centimeters of blood. In none of these cases was the patient known to be diabetic. The urea content was elevated in 7 cases, ranging from 19 to 114 mg. per hundred cubic centimeters of blood, with an average of 44 mg. The level of cholesterol was elevated to 320 mg. per hundred cubic centimeters of serum in 1 case. Moderate secondary anemia was present in 5 cases, and severe secondary anemia, in 2 cases.

Gastric extraction showed hyperacidity and a strongly positive benzidine reaction in 1 case. Duodenal extraction showed absence of bile both before and after the instillation of magnesium sulfate in 3 cases, a 4 plus reaction for blood in 1 case and no amylase in 1 case.

Roentgen examination of the gastrointestinal tract gave negative results in 5 cases; in 2 cases it yielded evidence suggestive of a lesion of the head of the pancreas.

Studies of the gallbladder showed no visualization in 4 cases. In 3 cases an opaque shadow of the gallbladder was seen in a flat roentgenogram.

While in some instances certain features are present with sufficient regularity to be suggestive of the primary lesion in the bile duct, yet because of the lack of any typical symptoms pathognomonic of the disease the diagnosis is not always clear. Such facts, of course, open a field for wide speculation, but it is not our purpose to delve any more into the subject, aside from stating that a correct diagnosis may be made only by careful history taking and by physical and laboratory examinations.

A correct clinical diagnosis of carcinoma of the distal portion of the bile duct was made in 5 of the cases, or 29.7 per cent. In a recent publication by Lieber, Stewart and Lund it was noted that a correct diagnosis was made in only 5.9 per cent of a series of 222 collected cases.

In the remaining 12 cases of our series the following diagnoses were made: cholelithiasis and choledocholithiasis, 2 cases; carcinoma of the head of the pancreas, 4 cases; carcinoma of the stomach with secondary involvement of the bile duct, 2 cases; acute cholecystitis, 2 cases; cholecystitis and cholelithiasis, 1 case, and carcinoma of the gallbladder, 1 case.

Not only is difficulty encountered in making a correct diagnosis on clinical examination of the patient, but often even after intensive exploration of the abdominal organs at the time of operation the true nature of the disease cannot be ascertained. Of 122 operative cases in Lieber, Stewart and Lund's series, an incorrect diagnosis was made at the time of operation in 39. In retrospect, the operative findings in our cases strongly suggest the correct diagnosis. They were overlooked, however, because in each case the main finding at operation pointed to a lesion elsewhere and not to the primary growth in the bile duct. Thus in 4 of the operative cases the lesion noted when the abdomen was opened was empyema of the gallbladder, and the operator, being satisfied as to the patient's ailment, refrained from any further exploration. It has been our experience that even at necropsy a correct diagnosis is not made in many instances until the biliary passages are widely opened and explored.

We wish to cite some of the case reports from our series as examples of the confusing clinical picture which these patients present both to the clinician and to the operator. Of 6 of the operative cases, the lesions in 2 were erroneously diagnosed as empyema of the gallbladder associted with cholangitis and hepatitis; in 2 others they were diagnosed as carcinoma of the head of the pancreas. In these cases they later proved to be carcinoma of the ampulla and papilla of Vater.

REPORT OF CASES

Case 1.—S. A., a 47 year old man, was admitted to the hospital complaining of anorexia, pain in the right upper quadrant of the abdomen, jaundice and pruritus of three months' duration. Seven years previously a resection of the ascending colon had been performed for carcinoma. The patient remained well until three months prior to his readmission to the hospital, when he first noticed pains in the upper part of the abdomen (especially after partaking of fatty meals), intermittent jaundice and clay-colored stools. There was no loss of weight.

Physical examination revealed him to be well developed and well nourished. He was moderately icteric. The right upper quadrant of the abdomen was tender, and the muscles were spastic. The liver was palpable 2 fingerbreadths below the costal margin. The icteric index was 33; the stools showed absence of bile for ten days, and then the bile reappeared in moderate amounts. The stools showed a strongly positive reaction to benzidine. A preoperative diagnosis of obstructive cholangitis, possibly of malignant origin, was made.

At operation an acutely inflamed noncalculous gallbladder was found. The bile ducts were normal to palpation, but the adjoining lymph nodes appeared

enlarged. A cholecystectomy was performed, and the pathologic diagnosis was acute cholecystitis. Three weeks after the operation a biliary fistula developed, and a cholangiogram taken through the fistulous opening revealed an obstruction of the papilla (interpreted as a calculus); the bile ducts were dilated. Repeated cholangiograms thereafter showed a distinct round shadow blocking the opening of the papilla. The fistula soon closed, the patient recovered rapidly, bile began to appear in the stools and the jaundice diminished. The patient was then discharged, apparently well. He was readmitted five months later because of the development of painless jaundice associated with clay-colored stools. A gastrointestinal roentgen series was reported normal (fig. 3).

Fig. 3.—Dilated common bile duct filled with dye. In the papilla is seen a distinct round shadow suggestive of stone formation.

At reoperation the common bile duct was found tremendously dilated. It presented, however, a point of obstruction at the papilla which prevented the passage of a probe. A grating noise similar to that produced by a stone was elicited on attempting to pass the instrument beyond this point. Attempts to recover the supposed stone through an opening in the duct failed. On transduodenal approach to the papilla there was no evidence of stone in the papilla or in the duct. A T tube was then inserted into the common bile duct, and the abdomen was closed. The patient failed to rally from the operation and died six days later.

At autopsy there was found a carcinoma of the papilla with extension to the duodenum. The duodenal mucosa immediately adjoining the papilla was widely ulcerated. There were regional metastases to the lymph nodes and to the pancreas.

The salient features of this case are, first, the acute onset of the disease and the finding of an acutely inflamed gallbladder at the first operation; second, the constant roentgen finding of a round shadow in the papilla, interpreted as representing a calculus; third, the long period between the acute attack of gallbladder disease and cholecystectomy and the appearance of symptoms caused by the papillary neoplasm, and last, the intermittent attacks of jaundice and associated symptoms of biliary obstruction present both before and after operation.

CASE 2.—H. T., a 68 year old man, was admitted to the hospital complaining of loss of weight for two months and icterus and pruritus for two weeks. One year previously he had had pains in the upper part of the abdomen radiating to the back. On physical examination the patient appeared cachectic and jaundiced. The edge of the liver was palpated at the umbilicus, and there was a suggestion of free fluid in the peritoneal cavity. Laboratory examination revealed the icteric index to be 132 and the value for phosphatase 30.9 units. The van den Bergh test elicited a direct immediate positive reaction. The urine gave a 4 plus reaction for bile. The stools were free of bile and showed a 4 plus reaction to benzidine. There was leukocytosis, with 13,000 white blood cells per cubic millimeter. A preoperative diagnosis of carcinoma of the common bile duct was made. At operation the liver appeared cirrhotic and cholemic and was adherent to the parietal peritoneum. The gallbladder was hidden by adjoining adherent loops of intestine and stomach. When the adhesions were separated and the gallbladder exposed, the latter was found to be thick walled and necrotic, and the cavity was distended with pus. The pancreas and duodenum felt normal. A cholecystostomy was performed, and a section of the gallbladder was removed for biopsy. The pathologic diagnosis was acute and chronic cholecystitis; a culture of the pus recovered from the gallbladder yielded Staphylococcus aureus and gram-negative organisms. The patient failed to rally from the operation and died three days later. At necropsy there was found a carcinoma arising from the papilla which extended upward to involve the wall of the bile duct.

Here again it is of interest to note the acute inflammatory process found in the gallbladder at operation, although clinically there were no signs or symptoms to indicate that such a condition existed. Moreover, the carcinoma of the duct was completely overlooked at the time of operation, although clinically there were signs and symptoms to indicate that such a condition existed.

CASE 3.—M. W., a 48 year old white man, was admitted to the hospital because of icterus, pruritus, parageusia and anorexia of two and a half weeks' duration; he had lost considerable weight. On examination, the patient appeared well developed and well nourished. He was icteric, and the skin was covered with scratch marks and purpuric spots. The liver was enlarged and firm; the gallbladder was palpable. The icterus index of the blood ranged up to 105, and the van den Bergh test showed an immediate positive reaction. The stools were free of bile and gave a positive reaction to the benzidine test. A flat plate of the gallbladder showed an opaque shadw, and there was no visualization of the gallbladder with the dye test. A series of gastrointestinal roentgenograms showed an increased duodenal sweep suggestive of tumefaction of the head of the pancreas.

At operation the liver was found enlarged, smooth and cholemic. There was hydrops of the gallbladder, but the lumen was free of stones. The pancreas was the seat of a large, hard mass. A cholecystogastrostomy was performed, and the abdomen was closed. The patient made an uneventful recovery. About sixteen months later he was readmitted to the hospital, because of chills and fever of five weeks' duration. He was markedly icteric, and the liver was enlarged to the level of the umbilicus. He was reoperated on, and the mass in the pancreas was still present. A new cholecystogastrostomy was performed because the stoma of the previous one appeared stenotic. The patient recovered from the operation, and on discharge he was free from symptoms and the icterus had disappeared. He was well for over two years; then he had chills, fever and jaundice at irregular intervals. The stools were frequently black. During the past five weeks he had been vomiting, and he had lost 20 pounds (9.1 Kg.) in weight. He was reoperated on, and the mass in the pancreas was still palpable. He died one day after the operation.

At autopsy there was found a carcinoma of the papilla of Vater with metastasis to the duodenum and the pancreas. The gallbladder was the seat of an acute suppurative process, and the pancreas in addition to the metastasis showed chronic pancreatitis.

Of particular interest in this case was the long duration of the growth (three years and eight months) with very little distant metastasis. Equally interesting are the inability of the surgeon to recognize the lesion in the papilla at the time of operation and the constant finding of a mass in the pancreas which was taken to be a carcinomatous growth and the cause of the patient's symptoms.

Case 4.—T. R., a 69 year old man, was admitted to the hospital complaining of recurrent attacks of jaundice, agonizing pains in the right upper quadrant of the abdomen and vomiting. For the past fifteen years he had been subject to attacks of epigastric pains which radiated to the right and to the back. Examination revealed nothing unusual aside from tenderness in the right upper quadrant of the abdomen. The impression was that he was suffering from a stone in the common duct. At operation there was found an acutely inflamed gallbladder containing a large calculus. The common bile duct was dilated and contained pus. A cholecystostomy and a choledochostomy were performed.

He was readmitted fourteen months later, because of jaundice and pruritus. The appetite was good, and there was no loss of weight. On examination he was found to be icteric. The liver was enlarged to 2 fingerbreadths below the costal margin. On reoperation the liver appeared cirrhotic. The common bile duct was dilated to 3 fingerbreadths. At the papilla there was palpated a firm mass the size of a peach stone, although the duct readily permitted the passage of a uterine forceps into the duodenum. A secondary cholecystostomy was performed, but the patient died nine days later.

In this case also the onset of illness was ushered in by an acute inflammation of the gallbladder, which finding was verified at operation. Because of these operative findings, thorough exploration of the duct at the time of the first operation was not done and the growth in the papilla was thus overlooked.

COMMENT

Carcinoma of the bile duct is as a rule a primary lesion and for a long time confines its growth to the duct. As the disease progresses, the growth extends into the muscular wall, but its tendency is to localize in the duct and not to metastasize. In some instances, however, it tends to extend into adjoining structures, especially into the duodenum, in which case it interrupts the muscularis mucosae and continues its course beneath it. When the duodenal mucosa is also involved in the tumor process, ulceration and secondary infection usually follow. These changes are responsible for a host of symptoms not directly related to the ductal growth itself but referable to the changes produced in the duodenal wall. Under such circumstances, for example, bleeding may take place from the ulcerated duodenal mucosa, and blood may appear either in the stools or in the vomitus. Thus, 2 of the patients in this series showed tarry stools which reacted positively to benzidine, and 1 showed gross hematemesis. Involvement of the pancreas, lymph nodes and more distant organs is a rather late occurrence. Metastasis takes place by direct extension and not by the usual route through the lymph or venous channels.

It is of interest to note in this connection that choledocholithiasis is observed to be associated with carcinoma of the bile duct far less commonly than with carcinoma of the gallbladder. In the present series carcinoma of the duct was associated with calculus formation in only 1 case.

In view of the present study of these cases and in correlation of the data with the various theories offered on the histogenesis of carcinoma of the bile duct, we are more inclined to consider these tumors as neoplasms arising from the ductal mucosa or, preferably, from the intramural sacculi of the duct. Throughout the entire series of cases the histologic picture presented by the tumors bore a striking morphologic resemblance to the sacculi described as occurring within the wall of the bile duct. It seems to us, therefore, that these neoplasms may be interpreted in terms of growths arising from this normal glandular structure.

As has been stated, there are no pathognomonic signs and symptoms of early carcinoma of the bile duct. Icterus, loss of weight, asthenia, anemia, anorexia, indigestion and vague abdominal symptoms may occur in various combinations and degrees. Melena is rare; occult blood in the feces is more frequent.

Diagnosis is invariably late, as it is dependent on the onset of symptoms, and it is well recognized that unfortunately the early symptoms of carcinoma of the bile duct are vague and are apt to be confused with those of other lesions of the upper part of the abdomen. There is of necessity a latent period between the earliest carcinomatous formation and the patient's awareness of something amiss, and the duration of

this period cannot be established at present. Owing to the low grade of malignancy of the growth, by the time the disease has produced symptoms of obstruction it is nearing the terminal stage. Early in this presentation the statement was made that the diagnosis of carcinoma of the biliary duct should not present any particular difficulty if the possibility is constantly kept in mind. While this statement holds true in a certain number of cases, exceptions may be made when adjoining organs also become involved. While it is also true that in some instances the signs and symptoms of carcinoma of the duct are rather typical, yet it is in cases presenting atypical features that one is apt to make a diagnostic error unless the condition is suspected and sought for. Among the more frequently encountered diagnostic pitfalls, perhaps empyema of the gallbladder heads the list. In this series, carcinoma of the terminal portion of the common bile duct was associated with an acute inflammatory process of the gallbladder in 6 cases. One can readily conceive the ease with which such a complication will develop if one bears in mind the close anatomic relation which exists between the gallbladder and the rest of the biliary system. It is generally conceded that when stagnation of bile occurs, as it is prone to do in the presence of biliary obstruction, there usually develops general cholangitis, and the gallbladder, being part of the biliary system, is necessarily involved in the inflammatory process. The occurrence of suppuration and empyema formation in the gallbladder is thus easily explained.

In reviewing the cases presented we note several clinical facts: First, in some of the cases of acute involvement the process was ushered in by the classic syndrome of sudden pains in the upper part of the abdomen, radiating to the back, often associated with chills and fever and suggestive of empyema of the gallbladder. In most of the cases these findings were corroborated at operation. Second, a group of cases existed in which there was no clinical evidence of involvement of the gallbladder, yet at operation empyema of the gallbladder was disclosed. Third, there was a group of cases in which the growth in the duct was situated so close to the orifice of the duct of Wirsung as to cause partial or complete obstruction of this duct and set up an inflammatory condition in the pancreas. Under such circumstances the pancreas at the time of operation felt massive and firm and gave the erroneous impression of carcinoma. Last, there was a notable group of ductal carcinomas which produced such extensive metastasis in the duodenum as to overshadow the primary growth in the duct.

Roentgen studies of neoplasms of the terminal portion of the common bile duct have not been fully exploited. The physician's armamentarium has not been exhaustively applied toward the differentiation of this lesion from other closely related diseases. Thus, in our series of 17 patients only 7 were subjected to a routine roentgen investigation

of the gastrointestinal tract for the purpose of ruling out possible malignant disease of this system. No particular attention was paid at the time of examination to any one portion of the intestinal tract. On restudying the roentgenograms for the purpose of this paper it was noted that in 5 of the 7 cases there were either definite or suggestive changes in the second portion of the duodenum. Since carcinoma of this portion of the duct is known to encroach on the lumen of the duodenum and occasionally to ulcerate or stenose this area, it is not startling to find roentgen evidence that such a condition existed. Closer attention to the second portion of the duodenum with this view in mind undoubtedly would yield more illuminating results. It is therefore suggested that in cases of a suspected lesion of the terminal bile duct a routine roentgen examination of the second portion of the duodenum should be carried out.

The prognosis of carcinoma of the bile duct is poor. If the condition is discovered early, resection is indicated. After symptoms of obstruction have developed, anastomosis around the growth, with a lower immediate mortality, is probably better than attempted resection, with a high immediate mortality and with slight chance of cure.

SUMMARY AND CONCLUSIONS

Seventeen cases of primary carcinoma of the terminal portion of the common bile duct with 8 autopsic observations are reported.

In the cases cited in this series, empyema of the gallbladder was frequently associated with this condition.

There are no pathognomonic signs and symptoms characteristic of carcinoma in the terminal portion of the bile duct. The symptoms are readily confused with other, closely allied conditions of the upper part of the abdomen.

Recognition of the pitfalls in the differential diagnosis of this condition and more frequent application of laboratory facilities, especially the roentgen rays, will reduce the high percentage of error in the clinical and operative diagnosis.

SEVERE HEMORRHAGE IN GASTRIC AND IN DUODENAL ULCER

A STUDY OF NINETY CASES

CRANSTON W. HOLMAN, M.D.
NEW YORK

In the past decade much has been written concerning the treatment of peptic ulcer which shows evidence of gross bleeding. During this period many physicians and surgeons have come to respect bleeding as a major complication of ulcer but as yet no uniformly accepted method of treatment has been established. Recently Meulengracht [1] published a report on a group of cases of bleeding peptic ulcer in which remarkably good results were obtained by treatment with a full purée diet. His conclusions favor a passive attitude toward this complication, and it is natural that physicians should welcome so simple a method of managing a condition which, with a great variety of treatments, has a mortality reported as ranging from 1 to 35 per cent.

This paper is an analysis of the observations on a group of 90 patients with bleeding ulcer. In general, these observations lead one to believe that a large percentage of patients with bleeding ulcers should be treated actively and at an early stage by surgical measures if a high mortality is to be avoided. It is evident from a study of these cases that up to the present time a definite program of treatment has not been followed; rather, the therapy has been determined by clinical examination of the individual patient. As a result of the findings in this group of patients, however, therapeutic measures have been formulated which, it is hoped, will help to improve results.

Complications of peptic ulcer apparently are becoming more rather than less frequent, in spite of increasing knowledge of the pathologic picture of this disease. Hemorrhage is by far the most frequent major complication, occurring in approximately one fourth of all cases, and except for perforation it is the most disturbing. Proper treatment rests on accurate diagnosis, knowledge of the pathologic picture, an appreciation of the value of the available methods of treatment and, when operative intervention is indicated, competent surgical handling.

From the Department of Surgery, the New York Hospital, and Cornell University Medical College.

1. Meulengracht, E.: Behandlung von Hämatemesis und Meläna mit uneingeschränkter Kost, Wien. klin. Wchnschr. **49**:1481, 1936.

DIAGNOSIS

The commonest cause of bleeding from the stomach or duodenum is peptic ulcer, and this diagnosis can usually be made after such other possible causes as esophageal varices, cancer and the hemorrhagic diatheses have been excluded. Except with a small group of patients who have had absolutely no antecedent history of pain or indigestion, it is practically impossible to say whether the bleeding comes from an acute or a chronic ulcer.

TABLE 1.—*Comparative Incidence of Acute and Chronic Ulcers Associated with Hemorrhage*

Author*	Cases of Acute Ulcer	Cases of Chronic Ulcer
Bulmer	15	23
Burger and Hartfall	15	30
Chiesman	13	17
Hellier	2	28
Nielsen [14]	16	39
Holman (New York Hospital series, this paper)	0	26
Total	61 (27%)	163 (73%)

* References in this and in the following tables not accompanied by superior figures will be found in the following list:

Aitken, R. S.: The Treatment of Profuse Bleeding from the Stomach and Duodenum, Lancet **1**: 839, 1934.

Armstrong, G. E.: The Wisdom of Surgical Interference in Hematemesis and Melena from Gastric and Duodenal Ulcer, Brit. M. J. **2**: 1087, 1899.

Babey, A. M., and Hurst, A. F.: The Incidence, Mortality and Treatment of Hemorrhage in Gastric, Duodenal and Anastomotic Ulcer, Guy's Hosp. Rep. **86**: 129, 1936.

Bulmer, E.: The Mortality from Hematemesis: Analysis of Five Hundred and Twenty-Six Cases, Lancet **2**: 168, 1927; Mortality from Hematemesis: Supplementary Analysis, ibid. **2**: 720, 1932.

Burger, G., and Hartfall, S. G.: Hematemesis in Peptic Ulcer, Guy's Hosp. Rep. **84**: 197, 1934.

Chiesman, W. E.: Mortality of Severe Hemorrhage from Peptic Ulcers, Lancet **2**: 722, 1932.

Conybeare, J. J.: Prognosis of Gastric and Duodenal Ulcer, Lancet **2**: 1017, 1935.

Davies, T. A. L., and Nevin, R. W.: Prognosis of Hematemesis: Statistical Review, Brit. M. J. **2**: 858, 1934.

Finsterer, H.: Operative Treatment of Severe Gastric Hemorrhage of Ulcer Origin, Lancet **2**: 303, 1936.

Fowler, W. M., and Hurevitz, H. M.: Bleeding Peptic Ulcer, J. Iowa M. Soc. **25**: 115, 1935.

Hellier, F. F.: Etiology and Mortality of Hematemesis, Lancet **2**: 1271, 1934.

Hinton, J. W.: Massive Hemorrhage in Peptic Ulcer, Ann. Surg. **101**: 856, 1935.

Umber, F.: Zur Prognose und Behandlung grosser Ulkusblutungen, Deutsche med. Wchnschr. **2**: 1265, 1935.

PATHOLOGIC PICTURE

While opinion regarding individual cases may vary, ulcers are commonly classified as either acute or chronic, depending on the pathologic findings, including the extent to which the walls of the viscus have been penetrated. As a rule, an acute ulcer remains superficial and does not penetrate the muscular layer of the stomach or duodenum, and for this reason it is not likely to be the source of severe bleeding. The greater incidence of hemorrhage in chronic ulcers is reflected in table 1, in which a group of cases observed at operation or at necropsy is listed.

Unfortunately, the nature of the pathologic change in a bleeding ulcer cannot be determined by its clinical manifestations. The important

question as far as treatment is concerned is whether a single bleeding point can be easily found at operation. Objection is sometimes raised to operation on the ground that the hematemesis may be caused by a capillary oozing from a diffusely congested mucosa, an idea popularized by White [2] in 1901. However, Bortz [3] in 1932, after a thorough search of the literature, could find only 52 cases in which this occurred, and in table 2 it will be seen that in all but a few of the 472 collected cases the source of the hemorrhage was readily established. In the great majority it was a large, eroded vessel in the base of the ulcer.

Eight of the fatal ulcers in this series showed such a large eroded vessel—the pancreaticoduodenal artery in 7 cases and the superior mesenteric artery in 1. These vessels protruded at the base of the ulcer

TABLE 2.—*Identification of Bleeding Point*

Author*	Autopsy	Operation	Total	Source of Bleeding Not Demonstrable
Aitken	10	21	31	2 (at operation)
Allen and Benedict [9]	8	..	8	0
Armstrong	9	..	9	0
Bulmer	38	..	38	0
Burger and Hartfall	30	..	30	0
Chiesman	45	..	45	1
Christiansen [7]	16	..	16	0
Finsterer	..	112	112	0
Fowler and Hurevitz	11	..	11	1
Hellier	30	..	30	0
Hinton	8	21	29	1 (at autopsy)
Nielsen [14]	55	..	55	0
Umber	..	29	29	1
Holman (New York Hospital series, this paper)	6	23	29	0
			472	

* References in this table not accompanied by superior figures will be found in the list appended to table 1.

through dense scar tissue, which precluded any retraction. Moreover, in several cases the vessels contained partially digested clots—the usual finding, according to Hunter.[4]

The location of the ulcer also plays an important role with respect to the occurrence of serious hemorrhage. Ulcers on the anterior wall of the duodenum rarely lead to dangerous hemorrhage, since there are no large vessels in this region; ulcers of the posterior wall possess the greatest capacity for serious or fatal hemorrhage because of their proximity to the superior and inferior pancreaticoduodenal arteries.

2. White, W. H.: Are Not Some Patients Said to Be Afflicted with Gastric Ulcer Really Suffering from a Different Disease? Lancet **1**:1819, 1901; Discussion on Hematemesis, ibid. **1**:1470, 1906.

3. Bortz, E. L.: Diffuse Hemorrhage from Stomach, Arch. Int. Med. **50**: 1 (July) 1932.

4. Hunter, J. B.: Action of Saliva and Gastric Juice on Clotting Blood, Brit. J. Surg. **16**:203, 1928.

These most intractable ulcers penetrate the pancreas, become calloused and erode into the large vessels, which are in direct contact with the posterior wall of the duodenum.

Contrary to the experience in European clinics, it appears that in the United States gastric ulcers are much less likely to be the source of fatal hemorrhage than are duodenal ulcers, but because of the vascularity of the stomach serious hemorrhage is always possible.

Most jejunal and marginal ulcers bleed to some extent, and occasionally, but not so frequently as with duodenal or gastric ulcer, the bleeding is fatal. Thus, Wright [5] reported 7 deaths in 124 cases of bleeding marginal or jejunal ulcer.

MORTALITY

Since one possible reason for the wide variation of published statistics on the prognosis and the mortality of bleeding peptic ulcer is the difference in the types of patients included, it should be stressed that this series includes only patients who were admitted to the hospital because of severe hemorrhage (hematemesis or melena or both) and who were proved beyond any reasonable doubt to be bleeding from a peptic ulcer. It consists of patients who were personally examined at the time of bleeding or who were interrogated at some later date to confirm opinions or data in the charts, as well as patients who came to necropsy. Finally, it is made up of the class of patients seen in a general ward service. The statistics of Hurst [6] support the impression that the class of patients seen in private practice is not so frequently subject to the severe complications of perforation and hemorrhage as that seen in charity practice.

Of the 90 patients, 12 (13.4 per cent) died in the hospital from hemorrhage. As is shown in table 3, this approximates the average mortality for cases reported from other clinics.

In table 4 the 12 fatal cases are summarized. Four of the 12 patients who died were never in a condition that warranted operative intervention. One of these was admitted to the medical service because of mental confusion and hemiplegia resulting from a cerebral accident. Seventeen days after admission symptoms of internal hemorrhage suddenly developed, and the patient died within twenty-four hours. Autopsy revealed a large, indurated duodenal ulcer. A second patient was admitted to the medical service in shock and died within twelve hours without hematemesis or melena; at autopsy a large, eroded pancreaticoduodenal artery was found in the base of a duodenal ulcer. A third patient, with

5. Wright, G.: Collective Inquiry into Gastro-Jejunal Ulceration, Brit. J. Surg. **22**:433, 1935.

6. Hurst, A. F.: The Incidence, Mortality and Treatment of Hemorrhage, Guy's Hosp. Rep. **86**:135, 1936.

amyotrophic lateral sclerosis and vague epigastric pain, was given a gastrointestinal roentgen examination. He subsequently showed signs of internal bleeding and in spite of repeated transfusions never recovered from the shock caused by the bleeding and died in thirty-six hours. A fourth patient entered the hospital after severe repeated hematemesis at home for three days. He had hyperpyrexia, became comatose twelve hours after admission and died within fifty hours. Four patients died after operative procedures undertaken with the hope of controlling hemorrhage and thereby averting a fatal outcome. Four died from hemorrhages that might have been controlled if operation had been performed. In spite of their acute loss of blood and anemia, in the case of each of the 4 there was a period after the initial hemorrhage when the patient's condition was sufficiently satisfactory to warrant operative intervention.

TABLE 3.—*Mortality*

Author*	Number of Cases	Deaths	Mortality, Percentage
Aitken	255	27	11
Allen and Benedict [9]	138	20	14.5
Babey and Hurst	82	4	5
Burger and Hartfall	137	31	22.5
Chiesman	191	48	25
Conybeare †	600	22	3.7
Christiansen [7]	289	23	7.9
Davies and Nevin	391	..	21
Fowler and Hurevitz	72	17	23
Hellier	202	30	14.8
Meulengracht [1]	273	3	1
Umber	433	41	9.5
Holman (New York Hospital series, this paper)	90	12	13.4

* References in this table not accompanied by superior figures will be found in the list appended to table 1.

† Conybeare stated that the mortality from hemorrhage in chronic ulcers is between 5 and 10 per cent.

With 1 exception, all the patients who died had hematemesis. The average time between the onset of bleeding and the death of the patient was eight days, but it should be emphasized that 6 patients died within four days. Christiansen [7] noted that in his experience and in the experience of others (Meulengrach;[1] Wood;[8] Allen and Benedict [9]) the average duration of bleeding before death was between thirteen and sixteen days; he concluded that the majority of patients die from some complication of hemorrhage rather than from the loss of blood itself. All the 8 patients not operated on in the present group died as a direct result of bleeding. In 2 of those who died the first and only hemorrhage

7. Christiansen, T.: On Massive Hemorrhage in Peptic Ulcer, Acta med. Scandinav. **84**:374, 1935; Uremia as Cause of Death in Massive Hemorrhage from Peptic Ulcer, ibid. **85**:333, 1935.

8. Wood, I. J.: Treatment of Hemorrhage, Brit. M. J. **2**:115, 1936.

9. Allen, A. W., and Benedict, E. B.: Acute Massive Hemorrhage from Duodenal Ulcer, Ann. Surg. **98**:756, 1933.

TABLE 4.—*Analysis of Deaths (New York Hospital Series)*

Number | Interval between | Post-

TABLE 4.—*Analysis of Deaths (New York Hospital Series)*

Patient*	Age	Type of Bleeding	Number of Hemorrhages	Operation	Interval between Onset of Bleeding and Operation	Condition	Cause of Death	Post-operative Duration of Life†	Bleeding Point	Autopsy	Comment
B.	27	Melena and hematemesis	1	Suture of bleeding point	29 days	Poor	Pneumonia	2 days	Posterior duodenal ulcer	+	
S.	34	Melena and hematemesis	5	Exploratory laparotomy	12 days	Poor	Bleeding	36 hr.	Jejunal ulcer	+	Bleeding continued from one unidentified jejunal ulcer; 3 jejunal ulcers present
F.	44	Melena and hematemesis	1	Gastric resection	17 days	Poor	Pneumonia	4 days	Posterior duodenal ulcer	0	Bleeding continued in hospital
J.	68	Melena and hematemesis	1	Gastric resection	7 days	Poor	Shock	17 hr.	Gastric ulcer	0	
W.	47	Melena and hematemesis	3	0	0	Poor	Bleeding	7 days	Jejunal ulcer	+	Superior mesenteric artery; started to bleed in hospital
R.	51	Hematemesis	1	0	0	Poor	Bleeding	6 days	Duodenal ulcer	0	Started bleeding in hospital while in bed; previous dismantling of posterior gastro-enterostomy
D.	59	Melena	1	0	0	Poor	Bleeding	60 hr.	Posterior duodenal ulcer	+	Started to bleed in hospital while in bed
S.	63	Melena and hematemesis	1	0	0	Poor	Bleeding	36 hr.	Posterior duodenal ulcer	+	Started to bleed in hospital while in bed
U.	28	Melena and hematemesis	1	0	0	Poor	Bleeding	4 days	Posterior duodenal ulcer	+	Patient improved for 2 days and then bled again while in bed
C.	34	None	1	0	0	Poor	Bleeding	24 hr.	Posterior duodenal ulcer	+	Massive hemorrhage; patient died 24 hours after onset
L.	49	Melena and hematemesis	2	0	0	Poor	Bleeding (uremia)	5 days	Posterior duodenal ulcer	+	
G.	43	Melena and hematemesis	1	0	0	Poor	Bleeding	4 days	Duodenal ulcer	0	

* All patients listed in this table were men.
† On duration of life after onset of bleeding.

followed immediately on completion of a barium roentgen study of the stomach and duodenum. It should, perhaps, be pointed out again that all the ulcers were chronic and that in all those examined at operation or necropsy a definite bleeding point was found, which usually was a branch of the pancreaticoduodenal artery in the base of a duodenal ulcer.

PROGNOSIS

Of all the factors to be considered in the prognosis of hemorrhage from ulcer, the patient's sex and age, the continuation or repetition of bleeding after hospitalization and the onset of bleeding while the patient is under strict medical care seem to be the most important.

In this group of patients only 19, or about 22 per cent, were women, none of whom died.[10] Most observers agreed that hemorrhage in young

TABLE 5.—*Mortality in Various Age Groups*

Author*	Age Groups							
	1-29 Years		30-39 Years		40-49 Years		50+ Years	
	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths
Allen and Benedict [9]	19	1	31	1	33	2	55	16
Bulmer	248	14	101	11	94	14	44	14
Burger and Hartfall	24	2	27	3	37	13	49	13
Hellier	37	6	45	4	61	7	59	13
Hinton	14	0	18	3	12	3	8	4
Meulengracht [1]	20	0	48	0	57	2	81	1
Holman (New York Hospital series, this paper)	10	2	20	2	30	3	30	5
Total	372	25	290	24	324	44	326	66
Mortality percentage	6.7		8.2		13.6		20	

* References in this table not accompanied by superior figures will be found in the list appended to table 1.

women rarely leads to death and the mortality is estimated at about 1 per cent.

The average age of the patients who recovered from the hemorrhage was 41 years and of those who died was 45.5 years—not so striking a difference as that found by Allen and Benedict,[9] who gave the respective average ages as 41.8 and 56.3. In table 5 a group of patients is analyzed to show the increasing mortality with advancing years. The higher mortality in the older groups is probably due to their greater susceptibility to complications as a result of loss of blood and also (in certain patients with arteriosclerosis) to loss of elasticity of the walls of the vessels. However, this increased mortality among the older patients has no relation to the chronicity of the ulcer, since the average duration of symptoms in the group who recovered was four and two-tenths years,

10. Since the writing of this paper a 67 year old woman has died from hemorrhage of a duodenal ulcer which had eroded the pancreaticoduodenal artery.

in contrast to four years in the group who died. In 1 patient who died the hemorrhage was the first indication of his disease, although autopsy revealed a chronic penetrating ulcer in the posterior wall of the duodenum.

The third prognostic indication, a very important one, is the continuation or immediate recurrence of bleeding after the patient has been hospitalized and treated for twenty-four to forty-eight hours. Table 6 illustrates the gravity of such uncontrolled bleeding.

Finally, of particular interest in the group of patients who died were 4 in whom hemorrhage occurred while they were receiving medical care for their ulcers in the hospital. In contrast, not one of the 78 patients who recovered had spontaneous hemorrhage while in bed in the hospital. Such a hemorrhage is a comparatively rare complication, and Hurst [6] stated that he has never witnessed it in a patient receiving strict

TABLE 6.—*Mortality in Relation to Response to Treatment*

Author*	Mortality After Satisfactory Immediate Response to Medical Treatment, Percentage	Mortality After Unsatisfactory Immediate Response to Medical Treatment with Continuation or Immediate Repetition of Bleeding, Percentage
Babey and Hurst	0	27
Burger and Hartfall	8.5	33
Chiesman	1.6	74
Davies and Nevin †	9.8	52.8
Holman (New York Hospital series, this paper)	6.4	46

* References in this table not accompanied by superior figures will be found in the list appended to table 1.
† Hematemesis from any cause.

medical therapy. As might be expected, all 4 patients had a chronic ulcer, and the 3 on whom necropsy was performed had large, gaping arteries in the base of the ulcer. The fourth patient had had a gastrocolic fistula repaired with a dismantling of the gastroenterostomy six months previously, and at that time a chronic duodenal ulcer was present.

As has been suggested by Ingegno,[11] studies of the blood urea may aid in the prognosis and also in determination of the degree of hemorrhage. Wood [8] found that a rising value for blood urea or a value above 80 mg. per hundred cubic centimeters is a sign of poor prognosis, although wide variations occasionally occur in a bleeding patient. In 2 patients in this series the values for blood urea were found to be high and to increase as the condition grew worse. Both patients died in a state similar to uremic coma.

11. Ingegno, A. P.: The Elevated Blood Urea of Acute Gastrointestinal Hemorrhage and Its Significance, Am. J. M. Sc. **190**:770, 1935.

THERAPY

Although most patients with bleeding ulcers should be given an opportunity to recover under conservative treatment, continued gross bleeding is more and more widely accepted as requiring surgical therapy. The specific indications for immediate surgical intervention are (1) continuous or repeated hemorrhage and (2) primary hemorrhage after the patient has been completely at rest in the hospital. Not only is the mortality in this class of patients (table 5) very high under conservative therapy (approximately 50 per cent), but in every patient in this series whose ulcer was visualized either at operation or at necropsy the bleeding vessel was so large that it is doubtful whether anything short of a direct attack on it could have controlled the hemorrhage.

Resection, when feasible, is the ideal procedure, and in this series no patient has had a recurrence of bleeding after such an operation. However, because of the patient's condition less formidable operations often are employed. It would seem wise always to make a direct attack on the bleeding point, although ligation of the vessels that lead to the ulcer occasionally is a successful alternative (von Haberer;[12] Allen and Benedict[9]). Gastroenterostomy should be performed only if obstruction is present, and control of the bleeding point should be attempted at the same time. In this series gastroenterostomies were performed on 4 patients because of bleeding coincident with obstruction, and all have remained perfectly well. Of 5 patients without obstruction, 2 have had recurrent hemorrhage after gastroenterostomy, a finding that coincides with the experience of others (Westermann;[13] Nielsen;[14] Ryle[15]).

Large amounts of blood should be available for transfusion during operation and particularly after control of the bleeding point. As much as 1 or 2 liters of blood should be given at this time, and as much again can be safely administered within the next twenty-four hours. When this regimen is followed, there need be little danger of a fatal outcome during or shortly after the operation. Postoperatively, careful feeding is essential, and vitamins should be given parenterally to patients whose diet has been deficient.

In this series of 90 patients, 24 were operated on: 8 during active bleeding, with 4 deaths, and 16 within four to six weeks after hemorrhage, without a death—a combined mortality of 16 per cent. All 4 patients who died after operation had failed to respond to a protracted

12. von Haberer, H.: Chirurgische Behandlung des Magen- und Duodenalgeschwures, München. med. Wchnschr. **80**:1577, 1933.

13. Westermann, J. J.: Surgical Aspects of Bleeding Gastric and Duodenal Ulcers, Ann. Surg. **101**:1377, 1935.

14. Nielsen, N. A.: About the Choice Between Medical and Surgical Treatment of Ulcus Ventriculi and Duodeni, Acta chir. Scandinav. **55**:57, 1923.

15. Ryle, J. A.: Failures of Gastric Surgery, Lancet **1**:890, 1934.

conservative regimen and when finally operated on as a last resort were extremely poor operative risks. Two of these died from pneumonia two days and four days respectively after gastric resection. One patient with several bleeding jejunal ulcers died from a continuation of the bleeding from one of the ulcers, which had not been found at the time of the operation. These deaths might have been avoided had the patients been operated on earlier, when they were in better condition. Patients rarely succumb during the operative procedure, and complications, such as pneumonia, peritonitis and uremia, are responsible for the great majority of postoperative deaths.

Of the 90 patients whose cases are reported here, some form of gastric operation had been done in the remote past on 22. Gastroenterostomy had been performed on 15, resection on 1 and simple closure of a perforated ulcer, pyloroplasty or a dismantling procedure on the remaining 6. Twelve of these 22 had never bled until after their initial operation, performed for the treatment of an uncomplicated ulcer. It would seem, therefore, that operation—particularly gastroenterostomy—performed on patients with ulcers that have never bled need not be expected to prevent future bleeding unless in the course of the operation the source of bleeding is eliminated.

Patients with ulcer who are admitted for symptoms other than bleeding but who give a history of hemorrhage in the past should be treated as are patients with uncomplicated ulcer. My experience, however, and that of others indicate that without surgical intervention which eliminates the ulcer the subsequent course is often unsatisfactory from the standpoint of both pain and tendency to recurrence of bleeding. Thus, 28 of 69 patients (40 per cent) followed after discharge from the hospital have shown unsatisfactory results, a figure that approximates the findings of Allen and Benedict [9] and those of Westermann.[13] Jordan and Kiefer [16] found that 70 per cent of patients who had had two or more hemorrhages were doomed to suffer another. When surgical therapy is undertaken for these patients, gastric resection is advisable, since this operation offers the best protection against future hemorrhage.

SUMMARY AND CONCLUSIONS

A review of the cases of 90 patients with serious hemorrhage from peptic ulcer is presented.

In over 98 per cent of patients subjected to operation or examined post mortem the bleeding point was easily located, and in most a large eroded vessel could be demonstrated.

16. Jordan, S. M., and Kiefer, E. D.: Complications of Peptic Ulcer: Their Prognostic Significance, J. A. M. A. **103**:2004 (Dec. 29) 1934.

The most important factors in the mortality are age, sex, immediate recurrence of bleeding after complete rest and onset of bleeding under a strict medical regimen.

Early operation is usually advisable for men over 40 years of age who have immediately recurrent or persistent bleeding after complete rest in bed. Operation is even more urgently indicated for patients who begin to bleed while at complete rest under a medical regimen.

Surgical procedures should not be used as a prophylactic measure against future bleeding for patients who have never bled.

Patients with a history of bleeding in the distant past should be treated similarly to those with uncomplicated ulcer. However, conservative treatment of patients with a past history of bleeding is unsatisfactory in from 40 to 70 per cent of cases.

Notices

SYMPOSIUM ON PERIPHERAL VASCULAR DISEASES

A symposium on peripheral vascular diseases, comprising at least eleven papers and an editorial, will be published in the February issue. The papers now scheduled have been written by Drs. Frank V. Theis and M. R. Freeland, Chicago; Alton Ochsner and Michael DeBakey, New Orleans; John Homans, Boston; Géza de Takáts and John C. Reynolds, Chicago; Irving S. Wright, New York; C. A. Moyer and W. G. Maddock, Ann Arbor, Mich.; R. H. Smithwick, Boston; Gordon Murray, Toronto, Canada; Louis G. Herrmann and Edward J. McGrath, Cincinnati; Walter F. Kvale, Lucian A. Smith and Edgar V. Allen, Rochester, Minn., and Leland S. McKittrick, Boston. The symposium has been compiled under the direction of Dr. Arthur W. Allen, Boston.

Editorial

PERIPHERAL VASCULAR DISEASE

During the past decade there has been widespread interest in disorders of the peripheral circulation. This has led to the establishment of special clinics for the study and treatment of these conditions in a large number of medical centers in the United States. In spite of the continued lack of accurate knowledge of the underlying causes, much has been learned regarding the care of patients suffering from inadequate arterial flow to the extremities. Most of the disorders resulting from this condition have certain common characteristics, and the same general principles of management can be applied to them. Although the types of disability encountered in patients suffering from peripheral lesions associated with diseased veins are different in many respects from those encountered in patients with narrowed arteries, their management has usually been taken over by the special clinics interested in the whole problem of peripheral circulation. Concentrated interest in such conditions has varied considerably in different localities as regards the departments of general medicine concerned. Internists, surgeons and various specialists under these main divisions have all played their part. Research has been carried out by a wide variety of investigators. This has resulted in a better understanding of the situation, with marked influence on the proper care of the patient.

Practitioners have become cognizant of the need of palpating the peripheral vessels in the lower extremities of patients whose complaints indicate the possibility of inadequacy of circulation. They have a better idea concerning the interpretation of their findings in this respect and can frequently classify the lesion if one is present. It has been learned that certain general measures of study and treatment apply to a large group of peripheral vascular disorders. The effect of associated generalized diseases, such as arteriosclerosis, and of diabetes on the vascular tree are more accurately interpreted. The influence of the sympathetic nervous system on the nutrition of the distal parts of the extremities is now recognized, although the mechanism of its irregularity is not often apparent.

Many remedies in the form of vasodilators and mechanical devices have been the natural development in this field. To a large degree these have proved disappointing, but under certain circumstances they have some merit. Since nearly any disease is improved under the detailed, special care of those particularly interested in a successful

outcome, one must be on one's guard against attributing improvement to a specific measure rather than to the natural effect of rest, position, hygiene, proper food, exercises and the elimination of harmful influences. For these reasons it is informative to withhold specific measures of treatment in many cases until a proper evaluation of the situation can be made. This often requires from one to two weeks of care and study in the hospital, especially for patients suffering from arteriosclerotic obliterative disease and thromboangiitis obliterans.

In the arrangement of the symposium presented in this issue, an attempt is made to cover as many of the phases of the problem as space permits. Many authorities who could have contributed much to the subject were, of necessity, not solicited. It is realized that for this reason the review may appear inadequate. It is intended to present some of the general principles as they are understood today and various research approaches that are being made in different localities in America.

ARTHUR W. ALLEN, M.D.